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THE MODIFYING ACTION OF CERTAIN DRUGS (AMINOPHYLLIN, NITRITES, DIGITALIS) UPON THE EFFECTS OF INDUCED ANOXEMIA IN PATIENTS WITH CORONARY INSUFFICIENCY

WITH REMARKS ON THERAPY*

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OPINION differs concerning the effects of certain drugs upon the coronary circulation.[1] Do the xanthines increase coronary blood flow, and thereby lessen the tendency to anginal paroxysms in patients with coronary sclerosis?[2-23] Do the nitrites afford relief by lowering systemic blood pressure, or is their action predominantly on the vessels of the heart?[24-29] Does digitalis, by causing constriction of the coronary arteries, increase the frequency and intensity of pain?[24, 30-35] The evidence, assembled both in clinic and laboratory, is conflicting. In patients, so many factors are known to influence the occurrence of cardiac pain that the degree of discomfort, or the amount of effort required to produce it, is unreliable as an index of the efficacy of a drug. The results of laboratory experiments are based upon observations made on normal animals, with the blood supply to the heart either undamaged or acutely obstructed. It seemed that if an objective, as well as a subjective, criterion could be applied in patients who suffered from anginal pain caused by an inadequate coronary circulation, some light might be thrown upon these matters.

In 1938, an apparatus was described for inducing oxygen want by enabling the patient to breathe a mixture containing a constant percentage of oxygen at a rate comparable to that of the normal pulmonary ventilation.[36] Early in 1939, using a mixture containing 10

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per cent oxygen and 90 per cent nitrogen, changes were described in the electrocardiogram following the induction of generalized anoxemia.[37] Criteria were evolved for normal and abnormal responses, and it was suggested that certain characteristic and definable alterations in the electrocardiograms could be used as an index of coronary insufficiency. In addition, a majority of the patients with spontaneous attacks of pain experienced similar discomfort within the twenty-minute period during which the low oxygen mixture was inhaled.

These clinical observations have received support from the recent experiments of Leslie, Scott, Jr., and Mulinos.[38] After ligation of a coronary branch in cats, the usual deviation of RS-T segments and modification of the T waves were noted in the electrocardiograms. When the form had returned to normal, at the end of from twelve to twenty-nine days, the induction of anoxemia resulted in the reappearance of "coronary" complexes in every instance.

METHOD

Using the technique to which reference has already been made,[36] the effect of various drugs on the time of occurrence of pain and on the form of the electrocardiograms was studied. The tests were performed, as a rule, at intervals of one week. Several controls were made, to establish a standard response and to accustom the patients to the apparatus. No untoward effects occurred. The following drugs were given: aminophyllin (theophyllin-ethylenediamine), by vein; nitroglycerin; aminophyllin, by mouth; lactose; erythrol tetranitrate; and digitalis. Because of the relatively long duration of the changes produced in the electrocardiogram by digitalis, this drug was the last in the series. Aminophyllin was chosen to represent the xanthine group because it is widely used, is available for intravenous injection, and has received favorable therapeutic comment. Erythrol tetranitrate was tested, in addition to nitroglycerin, on account of its prolonged effect. The subjects were unaware of the nature of the preparation given.

The variability with which anginal paroxysms occur is well known. Many factors, notably the emotional status, character and amount of work, and diet, influence both their severity and frequency. Besides, over a period of months or years, spontaneous variations in the course of symptoms, either for better or worse, are common. Accordingly, a relatively short time was chosen for the use of each drug, and no change was made in the customary mode of life of the individual. No special attention was paid to his account of symptoms in the time between tests, except to inquire for possible evidence of drug toxicity. Six of the ten patients were unemployed.

All tests were performed in the cardiographic laboratory, at least two hours after a meal, and with the room quiet and at a comfortable temperature. The patients were informed of the nature of the work and the reasons for repeated observations. All expressed interest in the results and cooperated willingly.

A control electrocardiogram was taken at the beginning of each test, with the mouthpiece in place and the patient breathing room air. The electrodes, including the one on the precordium, were kept in place throughout each experiment. Additional records were made at intervals of five minutes, and immediately on the appearance of pain, when this occurred. As soon as pain was felt the test was stopped, and the patient was allowed to breathe pure oxygen for a minute. If there was no discomfort, the test was terminated at the end of twenty minutes.

The blood pressure was recorded at five-minute intervals during each test. Heart rates were computed from the graphic records.

In serial electrocardiograms of patients with coronary sclerosis, taken over a period of weeks or months when no drugs were being administered, we have observed slight, but definite, changes in form, particularly in the T waves, without associated clinical evidence of cardiac infarction, or, indeed, of any circulatory disturbance of which the patient was aware. Such changes are often transitory and reversible within a short time. They probably are caused by alterations in the state of the coronary circulation. The level of the RS-T junctions tends to remain fixed, however, within narrow limits; a change of more than 1 mm. in any one lead is rare. For this reason, in addition to observing the effect of drugs on the time of occurrence of pain caused by induced anoxemia, the modifying action on the RS-T junctions in the four-lead electrocardiogram was studied.* This afforded an objective, as well as a subjective, index of effect. Deviation of the RS-T junction was taken as the difference in level between the point just preceding the initial deflection of QRS and the point immediately following its final deflection. The arithmetical sum of the RS-T deviations in all four leads, measured in millimeters, was used in the calculations. Changes in the form and direction of the T waves were also noted; but, though often striking, they did not lend themselves as readily to numerical calculation.

In computing the changes caused by drugs, it seemed proper to compare records taken at like moments in each experiment. For example, if pain appeared after five minutes of anoxemia in the controls, the electrocardiogram taken at that time was compared with one made after five minutes in all subsequent observations, even though the onset of pain was delayed or hastened because of drug action. Occasionally, observations were not made at precisely the same time after beginning the test as in the controls; when this occurred, the figures were corrected in proportion to the differences in the elapsed time. Such corrections were slight, and did not materially modify the results. A similar method was followed in dealing with changes in blood pressure and heart rate.

Because the functional state of the coronary circulation in a given individual is subject to variation, the results in the ten patients were pooled and averaged. In this way trends became apparent.

Aminophyllin, in doses of 0.48 Gm. (7½ gr.), in 20 c.c. of salt solution, was injected into the cubital vein during a five-minute period. The test was begun five minutes after the injection was completed. Two patients complained of a sense of warmth. Two had an intense desire to urinate before the test was completed.

Nitroglycerin was given in the form of a tablet of 0.0006 Gm. (1/100 gr.). The variety dispensed in tubes for hypodermic use was chosen because these tubes are tightly sealed. A fresh tube was opened every two weeks. The tablet was dissolved in the mouth after the control electrocardiogram had been taken; the induction of anoxemia was then begun immediately.

Aminophyllin, in doses of 0.2 Gm. (3 gr.), was put up in a capsule in the hospital pharmacy. One capsule was taken three times a day, after meals, and a fourth at bedtime, for one week. One patient complained of "indigestion" and one of insomnia. The difficulty in getting to sleep was abolished by discontinuing the dose at bedtime in this case.

Lactose, in doses of 0.2 Gm. (3 gr.), was placed in a capsule exactly like that containing aminophyllin, and the same dosage was followed.

Erythrol tetranitrate, in doses of 0.03 Gm. (½ gr.), was taken by mouth after the control electrocardiogram was made. The anoxemia test was begun thirty minutes later, and was thus carried out during the period of the drug's effectiveness.

*The precordial lead employed was the one designated as IVF by the American Heart Association.

Digitalis, in doses of 0.1 Gm. (1½ gr.), which is equivalent to 1 Hatcher-Brody cat unit, was given as a tablet three times a day on the first day and four times daily for the next three days, making a total of 1.5 Gm. in four days. The test was performed on the fifth day. There were no symptoms or signs of toxicity.

MATERIAL

The observations were carried out on ten patients with coronary sclerosis who had been followed in the hospital and outpatient department for months or years. They were selected because there seemed no doubt as to the correctness of the diagnosis, and because they were dependable and willing to participate in the study. In one case, observations on nitroglycerin, erythrol tetranitrate, and digitalis were not made because the patient moved out of the city before the series was completed. There were nine men and one woman. In age, they ranged from 47 to 69 years (average, 59 years). All suffered from spontaneous attacks of anginal pain and obtained relief from nitroglycerin. Three had hypertension, one a healed myocardial infarct, and one aortic insufficiency. In each case, the control anoxemia tests showed significant changes in the electrocardiograms. Nine of the ten patients experienced pain during the test; one, upon whom a paravertebral alcohol block had been performed eight years previously, went the full twenty minutes without discomfort. Case summaries are given at the end of the paper.

The results are based on eighty-six tests, and measurements of 739 electrocardiograms.

RESULTS

These are shown in Figs. 1 and 2.

Aminophyllin, by Vein.—The dosage was from 7 to 8 mg. per kg. of body weight. This caused a prolongation of 63 per cent in the time of appearance of pain. It is of interest that in one patient the pain appeared earlier than in the control. Perhaps the increase in cardiac work caused by the drug was greater than the augmentation in coronary flow.[39] Deviation of the RS-T junctions was diminished by 58 per cent. The T waves were modified significantly in seven of ten cases (Figs. 3 and 4). In a few instances, injection of the drug alone altered the form of the electrocardiogram (Figs. 3 and 4). Injection of an equal amount of salt solution in two cases did not alter the complexes. The heart rate decreased twice and showed no change eight times; in no case was the rate accelerated. The systolic blood pressure rose once, fell three times, and did not change four times. There was no constant relationship between changes in heart rate or blood pressure, the occurrence of anginal pain, and deviation of the RS-T junctions.

That the effects on pain and the electrocardiogram are caused by dilatation of the coronary arteries is suggested by previous observations. Fowler, Hurevitz, and Smith[15] noted that, after ligation of a coronary branch in dogs and subsequent intravenous injection of aminophyllin, the zone of infarction became smaller and the degree of cyanosis at its margins was lessened. Mahaim and Rothberger[40] found that, after coronary artery ligation in the dog, the injection of euphyl-

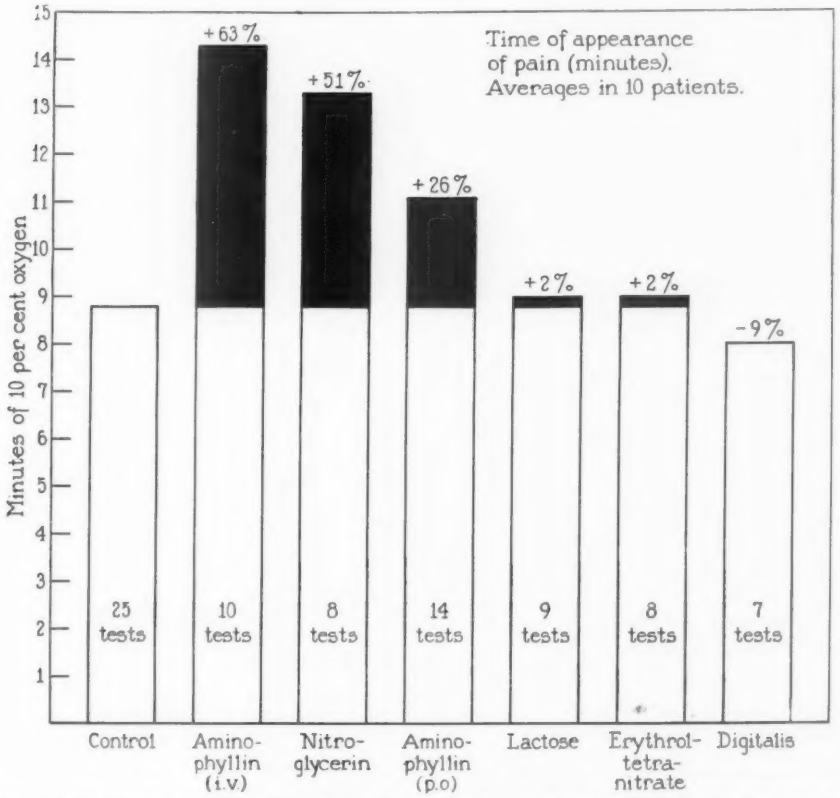

Fig. 1.—Modifying effect of drugs upon the time of appearance of cardiac pain caused by induced anoxemia.

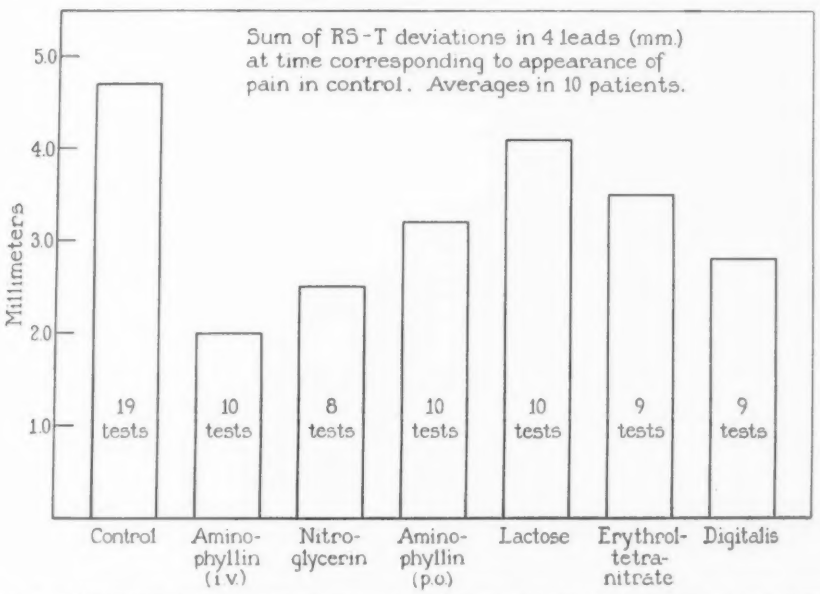

Fig. 2.—Modifying effect of drugs upon deviation of the RS-T junctions of the electrocardiogram caused by induced anoxemia.

lin (German aminophyllin), in doses of 23 mg. per kg., caused very little change in the color of the tissues surrounding the infarct. With double this dose, however, the infarct appeared smaller and cyanosis less intense. Four minutes after the injection, cyanosis again became more marked. After ligation and subsequent injection of 26 mg. per kg., the electrocardiogram showed relatively little modification. With 52 mg. per kg., the record returned to normal or approached it; but the effect passed off in two minutes. The authors concluded that euphyllin should be useful in the treatment of coronary insufficiency because it dilates the coronary arteries, but that relatively large doses are necessary and the action is of short duration.

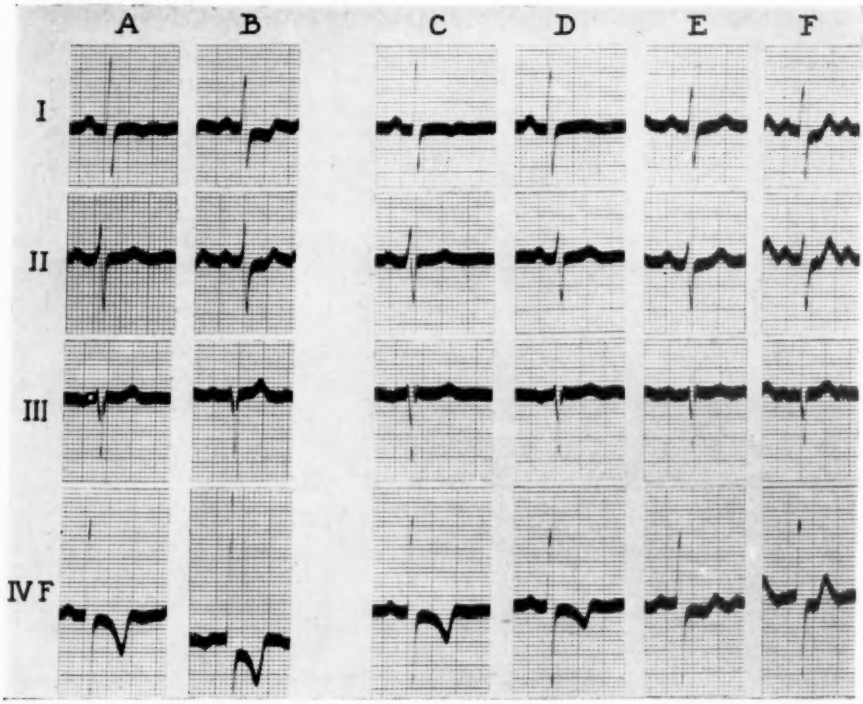

Fig. 3.—Case 8. Male, aged 54 years. *A*, control. *B*, after anoxemia for seven minutes; pain. *C*, control. *D*, immediately after intravenous injection of 0.48 Gm. aminophyllin. Anoxemia then started. *E*, after ten minutes. *F*, after twenty minutes; slight pain.

Similar observations were made by Laubry, Soulié, and Laubry.[41] They also noted, in dogs, that, in the neighborhood of an experimental infarct, collaterals dilated and became redder when aminophyllin was injected. The vasodilating action was maximal at the end of five minutes. While these changes in color were taking place, the modifications in the form of the electrocardiogram caused by coronary ligation disappeared. This was particularly true of the high take-off of the T wave. The doses necessary to cause these effects were from

10 to 25 mg. per kg. In some experiments, the S-T intervals altered their direction and fell below the isoelectric level. Significant changes also occurred in the T waves, which sometimes increased to two or three times their normal amplitude. The duration of action was brief, usually two to five minutes; exceptionally, it persisted for twenty minutes.

In dogs, using both intact animals and heart-lung preparations, Stoland and his associates[42] found that the average duration of increased coronary flow after the injection of aminophyllin was 21.6 minutes. They gave 5 to 6 mg. per kg., which corresponds to therapeutic doses in man.

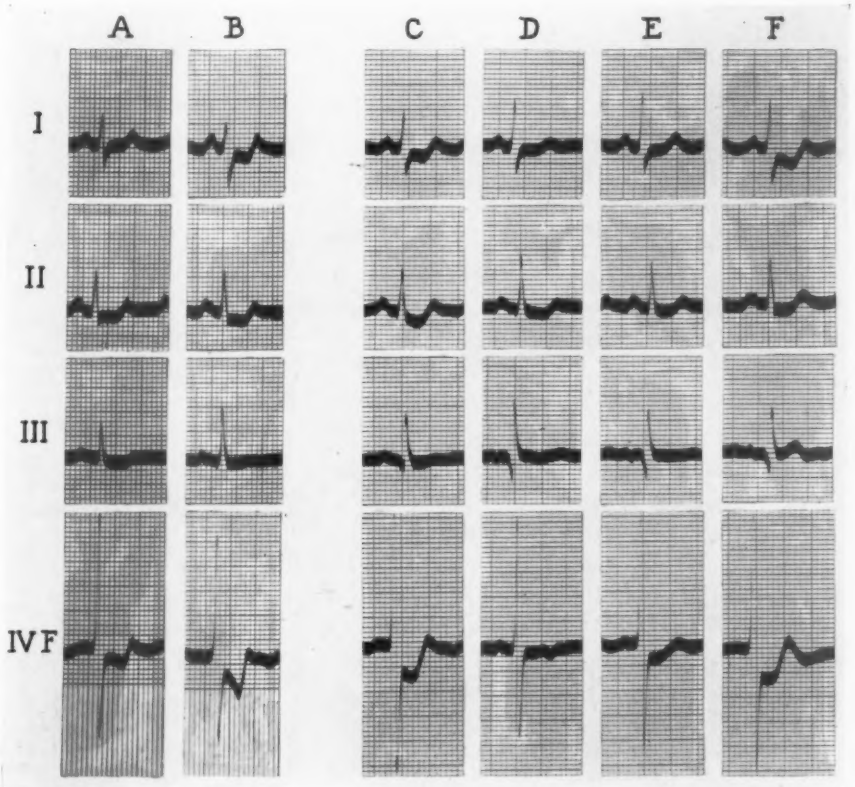

Fig. 4.—Case 9. Male, aged 52 years. *A*, control. *B*, after anoxemia for one and one-half minutes; pain. *C*, control; having spontaneous anginal attack. Intravenous injection of 0.48 Gm. aminophyllin given. *D*, immediately after completion of injection. Anoxemia then started. *E*, after five minutes. *F*, after nineteen minutes; pain.

In patients, Frey and Hess[43] observed, after the injection of deriphyllin (another theophyllin-amine compound), a change of the T wave toward normal and abolition of bundle branch block. The effects lasted for twenty minutes. Donath,[44] in one case, reported disappearance of bundle branch block for several hours after the injection of corphyllamin (Austrian euphyllin). This he ascribed to dilatation of

the coronary arteries. In a second case, transient bundle branch block could be made to appear, because, he believed, of an increase in heart rate caused by the drug. The increased work caused by tachycardia overbalanced augmentation in coronary flow.

One other effect of aminophyllin should be noted. Starr[39] has found that it increases cardiac output. Stewart* states that, in a dose of 0.48 Gm., when injected intravenously into patients, it increases the cardiac output about 30 per cent within five minutes after it is given. This may be another factor in producing augmentation of the coronary blood flow.[45]

Nitroglycerin.—This caused a prolongation of 51 per cent in the time of appearance of pain. Deviation of the RS-T junctions was diminished by 47 per cent. The T waves were modified significantly in six of nine cases (Fig. 5). The heart rate increased in three, decreased in two, and was unchanged in four. The blood pressure rose in two, fell in six, and was unchanged in one. There was no constant relationship between these various effects which would lead to the inference that they were dependent, one on another. Lengthening of the time of appearance of pain was by no means invariably accompanied by a fall in blood pressure; and the pressure occasionally fell when the appearance time of pain was not increased.

That nitroglycerin dilates the coronary vessels was demonstrated by Voegtlin and Macht[25] on isolated arterial strips, and by Meyer[24] and Schloss[26] on the intact heart. There has been difference of opinion, however, as to whether the relief of anginal pain is a result of coronary dilatation, lowering of systemic blood pressure, or both.[1] Our observations confirm those of Wayne and Laplace,[28] namely, that the effectiveness of nitroglycerin is due to dilatation of the coronary vessels and is not dependent upon a fall in blood pressure. This is also the conclusion of Sollmann.[29]

The one case in which the tolerance for anoxemia was diminished should be mentioned. Several instances have been reported in which administration of a nitrite increased anginal pain.[28, 46] It is probable that, in these patients, the rise in heart rate caused by the drug more than offsets the dilator effect on the coronary vessels.

Aminophyllin, by Mouth.—Taken four times daily for a week, this drug caused a prolongation of 26 per cent in the time of appearance of pain. Deviation of the RS-T junctions was diminished by 32 per cent. The T waves were modified significantly in seven of ten cases. The heart rate increased in three, decreased in three, and was unchanged in four. The blood pressure rose in three, fell in one, and was unchanged in four. There was no constant relationship between heart rate and blood pressure and the other criteria of its effect.

*Stewart, H. J.: Personal communication; to be published.

Both with respect to its action on the tolerance to anoxemia and modification of the electrocardiogram, aminophyllin by mouth was less effective than when it was given intravenously, and also less effective than nitroglycerin. It did, however, exert an appreciable influence. The concentration in the blood and tissues and the duration of action after oral administration are not known. Conceivably, when so taken in these doses, the drug exercises a dilator action on the coronary vessels when these are not too rigid because of disease, and when spasm of healthy collaterals is associated with sclerosis of part of the coronary bed.

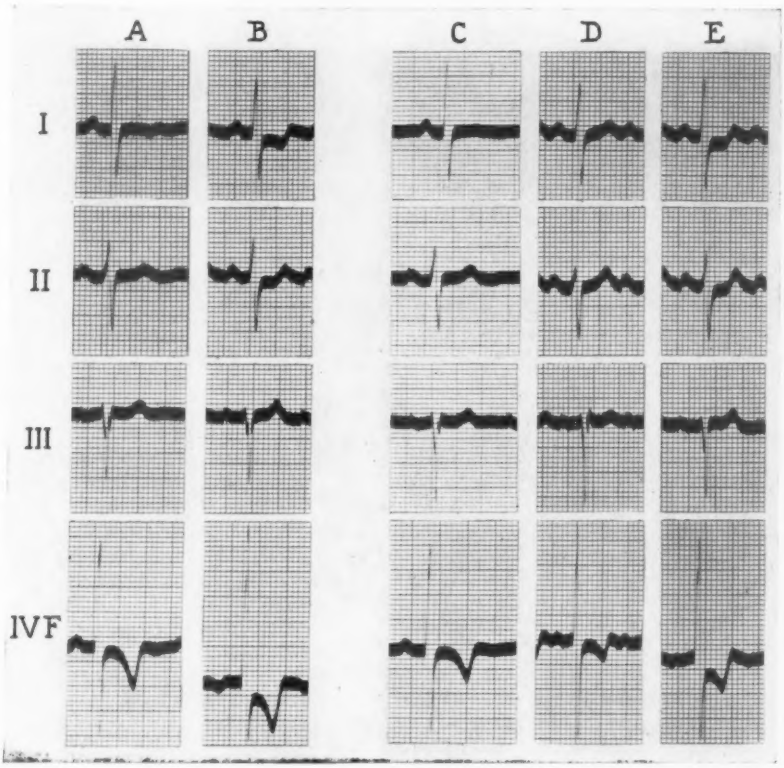

Fig. 5.—Case 8. *A*, control. *B*, after anoxemia for seven minutes. Pain. *C*, control. Nitroglycerin 0.6 mg. by mouth. Anoxemia then started. *D*, after seven minutes. *E*, after twenty-one minutes; pain.

Lactose.—No significant prolongation of the time of appearance of pain was observed. The increase of 2 per cent is negligible. Deviation of the RS-T junctions was diminished by 13 per cent. The T waves were modified in four of ten cases. The heart rate increased in two, decreased in three, and was unchanged in five. The blood pressure rose in four, fell in one, and did not alter in three.

The results with lactose serve to control those noted with aminophyllin by mouth. The differences, particularly in the pooled aver-

ages (Figs. 1 and 2), are definite. The difference of 13 per cent in RS-T deviation between controls and tests after administration of lactose may be taken to represent the approximate error of the method. It can be accounted for, in part, by spontaneous variations, to which allusion has already been made.

Erythrol tetranitrate.—In contrast to nitroglycerin, this caused no significant prolongation of the time of appearance of pain. The deviation of the RS-T junctions was diminished by 26 per cent. The T waves were modified in four of ten cases. The heart rate increased in one, decreased in three, and was unchanged in four. The blood pressure rose in five, fell in two, and did not alter in two. A fall in blood pressure occurred more frequently with nitroglycerin. The changes in the electrocardiogram, though not striking, were proportionately greater than the effect on pain, suggesting that the dilator action was not sufficient to modify appreciably the threshold for myocardial anoxia.

Erythrol tetranitrate, although more slowly absorbed than nitroglycerin, has a more prolonged action. According to Sollmann,[29] its effects appear only after half an hour and last from four to five hours. Its use has been suggested chiefly as a prophylactic against anginal attacks. Wayne and Laplace[28] found it effective in only three of nine cases, in all of which there was an especially good response to nitroglycerin. This drug, therefore, is of limited clinical value. It may be expected to increase the amount of effort which can be undertaken only in those cases in which this is already considerable. We have occasionally found it helpful in preventing nocturnal attacks, by having the patient take a dose just before retiring.[47]

Digitalis.—After the administration of 1.5 Gm. in four days, the usual changes in the RS-T junctions and T waves appeared in the electrocardiograms. With the anoxemia test, done on the fifth day, the time of appearance of pain was shortened by 9 per cent. The deviation of the RS-T junctions was diminished by 40 per cent. The T waves were modified in seven of nine cases. The heart rate increased in one, decreased in two, and was unchanged in six. The blood pressure rose in four, fell in one, and did not alter in four.

The increased susceptibility to pain in patients with coronary sclerosis after digitalis therapy has been stressed particularly by Fenn and Gilbert.[34] Gold and his collaborators,[35] in a recent paper, have stated that in patients who have anginal pain without congestive failure, the likelihood is negligible that the use of digitalis will, by a direct action on the circulation, increase or diminish discomfort. They also inferred that, because their patients were presumably unusually susceptible to cardiac ischemia, digitalis rarely, if ever, produces effective constriction of the coronary arteries in man.

Our results, though not striking, indicate that digitalis does, on occasion, increase the susceptibility to the pain induced by anoxemia.

On the other hand, the changes in the electrocardiogram suggest that coronary flow is increased, rather than decreased, by this drug. Too much emphasis cannot be placed upon the observed modifications of the RS-T junctions and T waves, because it is upon these portions of the electrocardiogram that digitalis itself exerts an effect. Whether the action of digitalis tends to lessen, or accentuates, changes in the form of the electrocardiogram which appear as a result of anoxemia is not clear. Other effects, notably alterations in cardiac output,[48] may play a part in bringing about the clinical result. Regardless of the mechanism involved, it appears that in certain patients with coronary sclerosis who are subject to anginal attacks, digitalis lowers the threshold for discomfort.

SUMMARY AND CONCLUSIONS

1. The modifying action of certain drugs upon the time of appearance of pain and upon the form of the electrocardiogram was studied after induced anoxemia. The results of eighty-six tests in ten patients who were subject to attacks of cardiac pain caused by coronary sclerosis were pooled, averaged, and compared with controls.

2. Aminophyllin, in doses of 0.48 Gm., injected intravenously, caused a prolongation of 63 per cent in the time of appearance of pain. RS-T deviation was diminished by 58 per cent. The T waves were modified in seven of ten cases.

3. Nitroglycerin caused a prolongation of 51 per cent in the time of appearance of pain. RS-T deviation was diminished by 47 per cent. The T waves were modified in six of nine cases.

4. Aminophyllin, when taken by mouth, caused a prolongation of 26 per cent in the time of appearance of pain. RS-T deviation was diminished by 32 per cent. The T waves were modified in four of ten cases.

5. Lactose caused no significant prolongation in the time of appearance of pain (2 per cent). The change in RS-T deviation was likewise small (13 per cent). The T waves were modified in four of ten cases.

6. Erythrol tetranitrate caused no significant prolongation in the time of appearance of pain (2 per cent). RS-T deviation was diminished by 26 per cent. The T waves were modified in four of nine cases.

7. Digitalis shortened the time of appearance of pain by 9 per cent. RS-T deviation was diminished by 40 per cent. The T waves were modified in seven of nine cases.

8. There were no constant relationships between changes in heart rate, blood pressure, the occurrence of anginal pain, and changes in the form of the electrocardiogram.

9. It would be premature to draw final conclusions concerning the possible value of aminophyllin in promoting the development of a col-

lateral circulation through the myocardium in the presence of coronary insufficiency. The effects of an intravenous injection are of short duration, lasting, on the average, twenty minutes. But it appears that, when taken by mouth in adequate doses, the drug exerts a beneficial action in certain cases of cardiac pain by causing dilatation of the coronary vessels. The result probably depends, in part, upon the anatomic condition and physiologic state of the coronary circulation. These vary in different patients, and in the same person from time to time. Criteria for the selection of suitable cases are not yet at hand; clinical trial must, for the present, serve as the basis for procedure.

10. Nitroglycerin dilates the coronary arteries of patients with coronary sclerosis; it is effective in relieving anginal pain for this reason, and not by virtue of the fact that it lowers systemic blood pressure.

11. Erythrol tetranitrate, although it apparently causes slight coronary dilatation, is not effective in raising materially the threshold for cardiac pain. It is, therefore, of limited value in preventing cardiac pain caused by coronary insufficiency.

12. Digitalis increases the tendency to pain in certain patients who are subject to anginal attacks. This effect does not appear to be due to coronary constriction. Whether it is caused by a modification of cardiac output, or by some other action of the drug, is not shown by these studies.

ABSTRACTED CASE REPORTS

CASE 1.—H. L. Unit No. 477070. A white man, a tailor, 65 years old, had had cardiac pain for three years. This was mostly in the back, particularly under the left scapula, and in the back of the neck. It was relieved by nitroglycerin, and was never substernal. There was some question in the mind of the examining physician whether the discomfort was cardiac in origin. Examination showed no cardiac enlargement, either on percussion or in the teleoroentgenogram. The electrocardiogram showed slight notching of the R wave in the three standard leads. The blood pressure was 135/70. Roentgenologic examination of the gastrointestinal tract showed nothing abnormal. The basal metabolic rate was normal. Roentgenograms of the spine showed no arthritis.

The control anoxemia test caused pain after nineteen minutes. There were deviation of RS-T in Leads I and IVF, and partial inversion of T in Lead IVF.

CASE 2.—C. G. Unit No. 566187. A white man, 58 years old, an unemployed butcher, for eight years had had occasional precordial pain which was relieved by nitroglycerin. There had been pain in the epigastrium for six days before admission to the hospital. He also had cramps in the right leg on walking. Examination showed no cardiac enlargement. The blood pressure was 102/58. The electrocardiogram showed sinus bradycardia, with a rate of 48. There was notching of R, and R in Lead IVF. The T wave was upright throughout, but was of low amplitude in Lead I. Roentgenologic examination of the stomach suggested the possibility of duodenal ulcer. Gastroscopic examination showed duodenitis and questionable duodenal ulcer. The epigastric discomfort improved greatly with treatment.

The control anoxemia test caused pain after three and one-half minutes. There were RS-T deviation in Leads I and IVF, and inversion of T in Lead IVF.

CASE 3.—A. S. Unit No. 459692. A white man, an unemployed cigar maker, 46 years old, complained of having had precordial pain for six weeks. He had been under observation for a number of years. The diagnosis was eosinophilic adenoma of the pituitary gland, with acromegaly, and toxic, nodular goiter. A partial thyroidectomy was done in November, 1935 (3 years before these cardiac studies were made). The heart was slightly enlarged to the left. The blood pressure was 120/86. The electrocardiogram showed slight left ventricular preponderance. T_1, T_2, and T in Lead IVF were upright; T_3 was inverted.

The control anoxemia test caused pain after sixteen minutes. There was RS-T deviation in Leads I and IVF. There was no significant change in the T waves.

CASE 4.—J. H. H. Unit No. 466904. A white man, a clerk on home relief, 68 years old, had had cardiac pain for three and one-half years. There was no cardiac enlargement on percussion or in the teleoroentgenogram. Roentgenographically, the aorta was seen to be tortuous. Typical, free, nonsyphilitic aortic insufficiency was present. The blood pressure was 210/50. The electrocardiogram showed only left ventricular preponderance. He probably had had a small coronary occlusion three years before the cardiac studies were made. At that time there was deviation of RS-T in Lead II; there were progressive changes in T_2 and T in Lead IVF.

The control anoxemia test caused pain after eleven minutes. There were RS-T deviation in Lead IVF, and partial inversion of T in Lead IVF.

CASE 5.—H. C. Unit No. 249119. A white man, 57 years old, an unemployed restaurant keeper, had had cardiac pain and dyspnea for seventeen years. He was given a paravertebral injection of alcohol in May, 1930, which was followed by partial relief. The patient also had hyperthyroidism, for which radiotherapy was given in 1930 and 1931, with return of the basal metabolic rate to normal and clinical improvement. In July, 1937, he had a coronary occlusion. Serial electrocardiograms had shown progressive changes in form since that date. The heart was moderately enlarged, the aorta dilated and tortuous. T_1 was inverted, T_2 diphasic, T_3 upright, and T in Lead IVF inverted. The blood pressure was 124/68. He was having only mild precordial discomfort on exertion.

This was the only patient who did not experience pain during induced anoxemia.

However, in the control tests, RS-T deviation occurred in Lead I, and the direction of T_1 and T in Lead IVF became reversed.

CASE 6.—H. A. Unit No. 376063. A white man, 69 years old, a retired stationary engineer, had had cardiac pain and dyspnea on exertion for six years. The heart was not enlarged. The blood pressure was 135/75. The electrocardiogram showed only left axis deviation.

The control anoxemia test caused pain in seven minutes. There were RS-T deviation in Leads I and IVF, and partial reversal of T_1, with complete reversal of T in Lead IVF.

CASE 7.—B. S. Unit No. 360149. A white man, 65 years old, a salesman, had had cardiac pain for six years. A teleoroentgenogram showed moderate left ventricular enlargement and a tortuous aorta. The electrocardiogram showed an inverted T_1 and a diphasic T_2. The blood pressure was 166/80.

The control anoxemia test caused pain in ten minutes. There was RS-T deviation in Leads I and IVF. No significant change occurred in the T waves.

CASE 8.—T. H. Unit No. 542971. A Japanese, 54 years old, an unemployed chef, had had cardiac pain on effort for eighteen months. A teleoroentgenogram showed slight enlargement of the heart, with moderate dilatation of the aorta. The electrocardiogram showed that T_1 was isoelectric, that T in Lead IVF was inverted, and that left axis deviation was present. The blood pressure was 148/84.

The control anoxemia test caused pain in seven minutes. There were RS-T deviation in Leads I and IVF, and partial reversal of the T in Lead I.

CASE 9.—I. R. Unit No. 473417. A white man, 52 years old, formerly the manager of a cafeteria, was now doing office work for the Works Progress Administration. Cardiac pain had begun four years earlier, and increased in severity. Hypertension was known to have been present for 20 years. The blood pressure was 210/120. A paravertebral injection of alcohol was given in November, 1936, which was followed by partial, though never complete, relief. The symptoms were aggravated in 1938 by the loss of his job and the necessity for performing physical work. The electrocardiogram showed varying amplitude of the T waves, but no evidence of serious myocardial damage. A teleoroentgenogram showed a slight increase in the transverse diameter of the heart, with moderate dilatation of the aorta.

The control anoxemia test caused pain in one and one-half minutes. There was RS-T deviation in Leads I and IVF. In this short time, the T waves were not modified. He died in the hospital of acute coronary occlusion, three months after these studies were completed.

CASE 10.—L. M. Unit No. 504326. A white woman, 60 years old, a housewife, had had cardiac pain for eighteen months. The heart was moderately enlarged to the left. The electrocardiogram showed a disphasic T_1 and inversion of T_2 and T_3. The blood pressure was 110/80.

The control anoxemia test caused pain after seven minutes. There was RS-T deviation in Leads I and IVF. There was no reversal in the direction of the T waves.

REFERENCES

1. Smith, F. M.: The Pharmacology of the Coronary Circulation. Chapter III in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, p. 109, The Macmillan Co.
2. Askanazy, S.: Klinisches über Diuretin, Deutsch. Arch. f. klin. Med. **56**: 209, 1895.
3. Breuer, R.: Zur Therapie und Pathogenese der Stenokardie und verwandte Zustände, Münch. med. Wchnschr. **49**: 1604, 1902.
4. Heathcote, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, J. Pharmacol. and Exp. Therap. **16**: 327, 1920.
5. Guggenheimer, H.: Zur Herzbehandlung bei Erkrankungen der Koronargefässe, Deutsch. med. Wchnschr. **49**: 1007, 1923.
6. Guggenheimer, H., and Sassa, K.: Über die Beeinflussung des Coronarkreislaufs durch Purinderivate, Klin. Wchnschr. **2**: 1451, 1923.
7. Smith, F. M., Miller, G. H., and Graber, V. C.: The Effect of Caffeine-Sodio-Benzoate, Theobromine Sodio-Salicylate, Theophylline and Euphylline on the Coronary Flow and Cardiac Action of the Rabbit, J. Clin. Investigation **2**: 157, 1925.
8. Dock, W.: The Use of Theobromine for Pain of Arteriosclerotic Origin, California and West. Med. **25**: 636, 1926.
9. Willius, F. A.: Newer Methods in the Treatment of Diseases of the Heart, Collected Papers of the Mayo Clinic **18**: 670, 1926.
10. Fisher, I., Guggenheimer, H., and Müller, E. A.: Über die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllinpräparate und Strophanthin nach Untersuchungen am Starlingschen Herz-Lungenpräparat, Deutsch. med. Wchnschr. **54**: 1584, 1928.
11. Musser, J. H.: Theophylline-Ethylenediamine in Heart Disease Associated With Pain, J. A. M. A. **91**: 1242, 1928.
12. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine-Base Diuretics on the Coronary Flow, Arch. Int. Med. **44**: 118, 1929.
13. Gilbert, N. C., and Kerr, J. A.: Clinical Results in Treatment of Angina Pectoris With the Purine-Base Diuretics, J. A. M. A. **92**: 201, 1929.
14. Evans, W., and Hoyle, C.: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, Quart. J. Med. **26**: 311, 1933.
15. Fowler, W. M., Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylene-diamine on Experimentally Induced Cardiac Infarction in the Dog, Arch. Int. Med. **56**: 1242, 1935.

16. Smith, F. M., Rathe, H. W., and Paul, W. D.: Theophylline in the Treatment of Disease of the Coronary Arteries, Arch. Int. Med. **56**: 1250, 1935.
17. Wiggers, C. J., and Green, H. D.: The Ineffectiveness of Drugs Upon Collateral Flow After Experimental Coronary Occlusion in Dogs, AM. HEART J. **11**: 527, 1936.
18. Riseman, J. E. F., and Brown, M. G.: The Medicinal Treatment of Angina Pectoris, Arch. Int. Med. **60**: 100, 1937.
19. Brown, M. G., and Riseman, J. E. F.: The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris, J. A. M. A. **109**: 256, 1937.
20. Gold, H., Travell, J., and Modell, W.: The Effect of Theophylline With Ethylenediamine (Aminophylline) on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, AM. HEART J. **14**: 284, 1937.
21. Gold, H., Kwit, N. T., and Otto, H.: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain, J. A. M. A. **108**: 2173, 1937.
22. Massel, H. M.: Clinical Observations on the Value of Various Xanthine Derivatives in Angina Pectoris, J. Lab. and Clin. Med. **24**: 380, 1939.
23. Master, A. M., Jaffe, H. L., and Dack, S.: The Drug Treatment of Angina Pectoris Due to Coronary Artery Disease, Am. J. Med. Sci. **197**: 774, 1939.
24. Meyer, F.: Über die Wirkung verschiedener Arzneimittel auf die Coronargefässe des lebenden Tieres, Arch. Anat. u. Physiol., Physiol. Abt. p. 223, 1912.
25. Voegtlin, C., and Macht, D. I.: The Action of Nitrites and Drugs of the Digitalis Group on the Isolated Coronary Artery, J. Pharmacol. and Exp. Therap. **5**: 77, 1913.
26. Schloss, K.: Über die Wirkung der Nitrite auf die Durchblutung des Herzens (Versuche am Herzen in situ), Deutsch. Arch. f. klin. Med. **111**: 310, 1913.
27. Smith, F. M.: The Action of the Nitrites on the Coronary Circulation, Arch. Int. Med. **28**: 836, 1921.
28. Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort, Clin. Science **1**: 103, 1933-34.
29. Sollmann, T.: Nitrites, Nitroglycerin and Other Alkyl Nitrates, A Manual of Pharmacology, 5th Ed., Philadelphia, 1936, p. 481, W. B. Saunders.
30. Bond, G. S.: Effect of Various Agents on the Blood Flow Through the Coronary Arteries and Veins, J. Exp. Med. **12**: 575, 1910.
31. Cushny, A. R.: Digitalis and Its Allies, New York, 1925, Longmans, Green and Co.
32. Bodo, R.: The Effect of Heart Tonics and Other Drugs Upon the Heart Tone and Coronary Circulation, J. Physiol. **64**: 365, 1928.
33. Fenn, G. K., and Gilbert, N. C.: Anginal Pain as a Result of Digitalis Administration, J. A. M. A. **98**: 99, 1932.
34. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**: 668, 1932.
35. Gold, H., Otto, H., Kwit, N., and Satchwell, H.: Does Digitalis Influence the Course of Cardiac Pain? A Study of 120 Selected Cases of Angina Pectoris, J. A. M. A. **110**: 859, 1938.
36. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1938.
37. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. Med. Sci. **197**: 241, 1939.
38. Leslie, A., Scott, W. S., Jr., and Mulinos, M. G.: Effect of Anoxemia Upon Electrocardiogram of Cats After Coronary Ligation, Proc. Soc. Exp. Biol. and Med. **41**: 652, 1939.
39. Starr, I., Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N., and Eagle, E.: A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work and Size; on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Invest. **16**: 799, 1937.
40. Mahaim, I., and Rothberger, C. J.: Ueber die Wirkung von Euphyllin beim experimentellen Koronararterienverschluss, Helvet. Med. Acta **2**: 687, 1936.
41. Laubry, C., Soulié, P., and Laubry, P.: Action de la Theophylline-Éthylènediamine sur la Circulation Coronarienne, Arch. des Mal. du Coeur et des Vaisseaux **30**: 265, 1937.

42. Stoland, O. O., Ginsberg, A. M., Loy, D. L., and Hiebert, P. E.: Studies on Coronary Circulation. IV. A. The Duration of the Coronary Dilator Action of Theophylline Ethylenediamine, J. Pharmacol. and Exp. Therap. **51**: 387, 1934.
43. Frey, J., and Hess, W.: Klinische und experimentelle Untersuchungen über Deriphyllin, Ztschr. f. d. ges. exp. Med. **101**: 509, 1937.
44. Donath, F.: Über inkonstanten Schenkelblock und über die Wirkung von Corphyllamin auf das Herz, Ztschr. f. klin. Med. **132**: 802, 1937.
45. Wiggers, C. J.: The Physiology of the Coronary Circulation. Chapter II in Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, p. 57, The Macmillan Co.
46. Wood, F. C., and Wolferth, C. C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47**: 339, 1931 (Case 4).
47. Levy, R. L.: The Drug Treatment of Heart Disease, Ann. Int. Med. **11**: 1946, 1938.
48. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of Digitalis on the Output of Blood From the Heart. III. Part 1. The Effect on the Output in Normal Hearts. Part 2. The Effect on the Output of Hearts in Heart Failure With Congestion, in Human Beings, J. Clin. Invest. **11**: 917, 1932.

ARTERIOSCLEROSIS OF THE CORONARY ARTERIES AND THE MECHANISM OF THEIR OCCLUSION

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INTRODUCTION

THE recent advances in our knowledge of diseases of the coronary arteries have effected a reconsideration of the subject of arteriosclerosis. Old beliefs have been re-emphasized and new concepts proposed concerning the pathogenesis of arteriosclerosis, particularly of the coronary arteries, and the mechanisms involved in thrombosis of these vessels. The question of intramural vascularization—its morphogenesis, its association with arteriosclerosis, its causal relationship to intramural hemorrhage—has been posed, and, to some extent, answered. For many years the formation of a thrombus on an arteriosclerotic plaque was considered the sole cause of coronary closure. Studies of the last few years, however, have indicated that intramural hemorrhage in a sclerotic artery is an important factor in the production of such a lesion. This has been identified either as an immediate etiologic factor in acute occlusion by a massive intimal hematoma, or as a precipitating agent in thrombosis of the lumen of the vessel. In view of the former, clinically, at least, it has become no longer strictly correct to speak of that catastrophic incident in arteriosclerosis of the coronary arteries as "acute coronary thrombosis," but rather as "acute coronary occlusion," and it appears that the ultimate differentiation must rest entirely upon the histologic interpretation. In view of the latter, it is important to ascertain, in a large group of cases, the frequency of occlusion caused by intramural hemorrhage, and to compare it with the incidence of occlusion due to other causes.

It is our purpose in this paper to evaluate objectively and critically the above problems and factors as they occur in a series of 100 unselected autopsy cases of acute occlusion of the coronary arteries. The clinical and forensic implications of these questions are patent. In addition, we shall review briefly the pertinent literature. The results of the study of the more general features of acute coronary artery occlusion and myocardial infarction will be presented in a subsequent publication.[1]

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MATERIAL AND METHODS

The material included in this study consists of 100 hearts which at autopsy showed evidence of recent occlusion of the coronary arteries, either by thrombosis or by massive hemorrhage into their walls, or both. Particular attention was paid to the relative importance and frequency of intimal hemorrhage and of primary thrombosis on an arteriosclerotic plaque in the pathogenesis of coronary artery occlusion, and also to the relationship between the extent of mural vascularization, hemorrhage, and arteriosclerosis. The nomenclature employed in this investigation was adopted from Spalteholz[2] and Gross.[3]

The coronary arteries and their branches (Table I) were sectioned transversely, at intervals of one to three millimeters, after fixation in formalin or Kaiserling or Jores solutions. Sections were made serially, or at very close intervals, for microscopic study of all arteries showing occlusion, of all vessels in which there was gross evidence of thrombosis, and of some of the arteries with nonoccluding intramural hemorrhage. Many segments were also taken for histologic examination from coronary arteries which showed variable degrees of arteriosclerosis. All blocks were embedded in paraffin. It is to be noted that in a fixed heart the vessels occasionally contain coagulated blood elements, which is a consequence of fixation. When such an area was discovered, it was routinely examined microscopically to ascertain whether or not ante-mortem thrombosis of the vessel had occurred. The histologic preparations were stained with hematoxylin-eosin; the Weigert-elastica-Van Gieson combination, the Lepehne hemoglobin stain, the Weigert fibrin, and the Bielschowsky silver impregnation method were used when indicated. All of the hearts were examined by us personally.

We also investigated the relative frequency of arteriosclerosis and recent occlusion of the various portions of the coronary artery tree. The degree of arteriosclerotic involvement of the ascending aorta and sinuses of Valsalva and the relationship of such changes to the coronary ostia were ascertained. The latter data will be the subject of a subsequent report.[1]

DISTRIBUTION OF ARTERIOSCLEROSIS

In general, many portions of the arterial tree, except the intermuscular branches, revealed varying degrees of arteriosclerotic thickening. In eighty-five instances the anterior descending branch of the left coronary, and, in seventy-one cases, the left circumflex artery showed severe intimal thickening and a corresponding degree of narrowing of the lumen. The right coronary artery was found to be severely affected by arteriosclerotic changes in seventy-six instances. The anterior descending branch of the left coronary artery most commonly disclosed severe sclerotic changes, but when these data are subjected to statistical interpretation according to the "hypothesis of equal frequencies," it becomes evident that these slight numerical variations are not significant. Hence it may be stated that severe arteriosclerosis occurs in these three major vessels with equal frequency.

It is interesting that, with respect to the secondary coronary branches, in forty-eight cases the primary division of the anterior descending branch of the left coronary artery showed severe arteriosclerosis, whereas in twenty-six instances this was present in the branch of the left coronary artery which runs to the obtuse margin of the heart. The degree of involvement of the remainder of the main arterial stems and their

TABLE I

INVOLVEMENT OF CORONARY ARTERIES IN ACUTE CORONARY ARTERY OCCLUSION (100 POST-MORTEM CASES)

	LEFT CORONARY ARTERY							RIGHT CORONARY ARTERY					
	LAD	R1°	R2°	LC	VSA	MO	VSP	RC	VDA	MA	VDP	SLP	VSP	TOTAL
Acute Occlusion	56	15	0	27	2	7	1	61	1	0	0	2	0	172
Severe Sclerosis (3 to 4+)	85	48	11	71	19	26	3	76	9	5	2	18	3	376

Branches of the Left Coronary Artery:
LAD—Anterior descending branch
R1°—Primary branch of LAD
R2°—Secondary branch of LAD
LC—Left circumflex branch
VSA—Branch to anterior left ventricle
MO—Branch to the obtuse margin
VSP—Branch to the posterior left ventricle

Branches of the Right Coronary Artery:
RC—Right circumflex
VDA—Branch to anterior right ventricle
MA—Branch to the acute margin
VDP—Branch to posterior right ventricle
SLP—Posterior descending branch
VSP—Branch to posterior left ventricle

Three- and four-plus sclerosis indicates arteriosclerosis with moderately severe narrowing, to almost complete obliteration of the lumen, respectively.

branches is indicated in Table I. These observations are in accord with those of Wolkoff[4] and Clawson.[5] Although arteriosclerosis is known usually to produce characteristic narrowing of the lumen of the segment of artery affected, there were three instances of diffuse "tubular" dilatation of the lumen despite definite arteriosclerotic involvement. Karsner[6] and Kutschera-Aichbergen[7] have also alluded to this possibility.

The lack of thickening of the intermuscular branches of the coronary arteries in arteriosclerosis has been noted by Wolkoff,[8] Saphir, et al.,[9] Bork,[10] Glomset,[11] and by us. Sutton and Brandes,[12] however, described sclerosis of intermuscular arteries in forty-two of their forty-nine cases of coronary arteriosclerosis. Only when there was widespread scarring of the myocardium did we note, in our series, any sclerotic involvement of the intermuscular divisions—and this was observed only in the vicinity of the scar. In but four cases did we find a moderate degree of arteriosclerosis of intermuscular arteries unassociated with any neighboring fibrosis.

MORPHOLOGIC CHARACTERISTICS OF ARTERIES

Microscopic study of the arterial walls revealed the well-known changes caused by arteriosclerosis.[4, 9, 10, 13, 14, 15] The intimal layer was most commonly and most severely affected. There were variable degrees of fibrotic thickening, fatty changes, collections of large fat-bearing macrophages, so-called atheromatous "abscesses," foci of calcification, and, occasionally, definite bone formation.

Distribution of Intramural Vascular Tree.—Associated with the sclerotic plaque there were cross sections of capillaries which traversed both degenerative and fibrotic zones and also appeared along the borders of calcific or bony plates. The number of capillaries varied greatly. They appeared most abundant in places where the fibrosis of the intima was only moderate and loose, and in the neighborhood of fatty plaques. Frequently, delicate capillary channels were found interspersed among the fatty vacuoles and between fat-bearing macrophages. The mural channels were least common in the vicinity of calcified and ossified plaques. In one case of bone formation, however, the capillaries were abundant. The arterial intramural vessels were extremely sparse, and occasionally totally wanting in the region of an atheromatous "abscess." Here their paucity was characteristic and macroscopically predictable, and it appeared to us that the extent of such "abscess" formation was inversely proportional to the degree of vascularization. Leary[15, 16, 17] noted the presence of such atheromatous "abscesses" ("atherocheuma" —Leary) particularly in older persons, and attributed their formation to a decreased nutritive supply and to the absence of fibrosis. He expressed the opinion that secondary rupture of these abscesses into the lumen of the artery was followed by thrombosis. He maintained, further, that in younger persons the tendency to fibrosis of the original intimal lipoid accumulations was greater, and that these large necrotic lesions, therefore, do not occur.

Although atheromatous abscesses are more common in the aged because arteriosclerosis is usually more advanced in this group, we have also observed that they occur in younger persons. In both groups there appeared to be the same inverse quantitative relationship between the extent of vascularization and the degree of intimal degeneration and necrosis. It becomes apparent that when intimal vascularization does not keep pace with fatty change and fibrous intimal thickening, the nourishment of the plaque will become so impaired that necrosis of the area must ensue (Fig. 1). Bruening[18] offered the view that in a normal artery the intima is nourished from the lumen, whereas in arteriosclerosis, when thickening of the intima has occurred, there is an increased demand of the intima for nourishment from the vasa vasorum, and that interference with this source of supply may induce intimal necrosis. Jucker,[19] on the other hand, did not attribute much etiologic significance to the vascular supply in the formation of such foci of necrosis, but felt that the necrosis of the intima in arteriosclerosis was the direct effect of a toxic agent. In evidence of such a contention, perhaps, is the well-known, widespread occurrence of arteriolar necrosis in cases of malignant hypertension. Whether or not these are related to a primary, severe, spastic, vascular phenomenon, with concomitant ischemia of the wall, or are the sequelae of a direct toxic mechanism, has not yet been ascertained in these cases. We believe, with Klemperer and Otani,[20] that the former is the more significant factor.

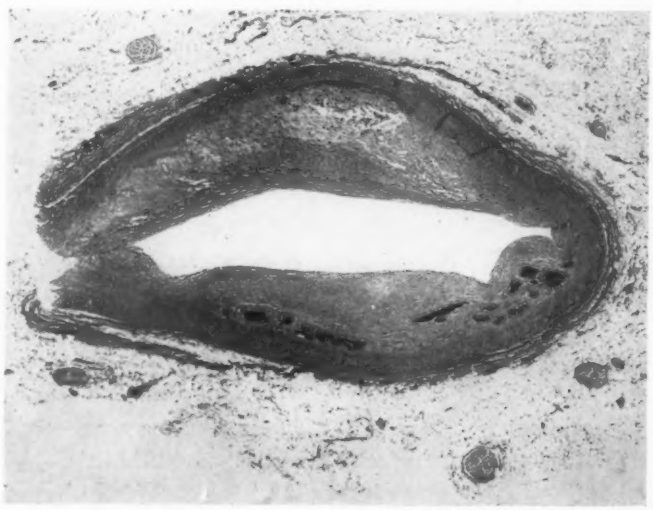

Fig. 1.—Low power photomicrograph shows the relationship of the vascular supply to severe intimal degeneration. Note the conspicuous absence of vascularization in the region of the "abscess" and rich vascular supply of the opposite fibrotic plaque.

The question of the distribution of the capillary circulation of the arterial wall has lately come into prominence as a result of the work of Leary, Paterson, Winternitz and his co-workers, and Wartman. Al-

though it has long been recognized[21] that there is a vascular pattern within human vessels, the significance of such a network within the walls of arteries has been clarified only within recent years. Capillaries stemming from the vasa vasorum have been described within the outer layers of the media in the medium-sized arteries of man,[22, 23] and have been observed by a few within the inner portions of the media.[24, 26, 38] The majority of investigators, however, favor the view that in the normal artery there is no distinct intimal capillary circulation, and that the nutrition of the intima is furnished primarily by imbibition from the main lumen, and secondarily from the vessels which have penetrated the medial layer.[27] It has been generally conceded that this distribution of capillaries occurs in the walls of normal arteries, and that only occasionally may vessels derived from the medial vasa penetrate into the intimal layer in healthy vessels.[28, 29] Gross and his co-workers,[30] however, have stated categorically that vasa vasorum are not found within the media of normal arteries. Our own studies have confirmed this opinion. We did not encounter any instance of a normal artery in which medial capillaries were histologically demonstrable.

A number of observers[26, 14, 4, 31] have referred to the vascularization of fibrous intimal plaques and the media of the arteries in arteriosclerosis, and have looked upon such a development as part of the arteriosclerotic process. More recently, Leary[16] described an intimal capillary network which communicated with the main arterial lumen in four of twenty-one cases of arteriosclerosis which he studied. Paterson, in a number of reports,[32, 33, 34] has emphasized the significance of the vascular pattern within the walls of sclerotic arteries and its relationship to thrombus formation. The etiologic association of an intramural capillary circulation with diseases of the vessel wall had been previously alluded to by Risse,[21] Koester,[35, 36] and others.[23, 29, 22, 37, 38, 39, 40, 41] These investigators were of the opinion that either inflammatory vascular lesions or arteriosclerotic degenerative changes, or both, were caused by interference with the blood supply from the vasa vasorum. For a complete discussion of the development of the earlier anatomic and etiologic concepts of an intramural vascular circulation the reader is referred to the review by Ramsey.[42]

Winternitz and his co-workers[41, 43] have written a monograph on the relationship between vascularization and arteriosclerosis. These authors, as a result of their own studies, and the recorded observations of the existence of a rich intimal capillary circulation in the arteries of animals, have assumed that a similar network exists within the intima of normal human coronary arteries, although they stated that technical methods have not been sufficiently developed to demonstrate it. Using this assumption, together with their observations on man, Winternitz and his associates formulated the belief that vascularization may pre-

cede the development of arteriosclerosis, and that the alterations in this vascular supply may occur prior to the degenerative processes within the intima.

In a large number of cross sections of normal coronary arteries which we examined in an attempt to determine morphologically the distribution of a capillary circulation, we never observed intimal vascular channels. Whenever vascular channels were found within the intima we could always prove that sclerotic alterations were present. This is in agreement with the observations of Leary, Paterson, and others.[14, 30] It should be stressed at this point that the vascularization which is noted in the region of intimal plaques is often so prolific that capillary overgrowth may occur, with extension of the newly formed vessels from the sclerotic to the adjacent unaffected portions of the artery. Consequently, before the possibility of the existence of intramural channels in so-called normal sections of the arterial wall can be accepted unequivocally, it is essential to investigate the status of the neighboring zones.

Winternitz and his associates have further suggested that the lipoid deposits situated within the intima may be derived from extravasated blood, and that the primary change, therefore, is caused by alterations in the mural vascular tree. As was previously intimated by Aschoff,[27, 44] Bork,[10] Wolkoff,[4] Ehrich and his coworkers,[45] and Leary,[15] the impression was gained in our studies that intimal lipoidosis or thickening is the earliest alteration in the intimal collagen, and that it occurs primarily without any relationship whatsoever to previous vascularization or hemorrhage. Like others[46, 47] before us, therefore, we have come to consider vascularization of the intima, and also of the media, as a response to the degenerative and proliferative phenomena of arteriosclerosis, and that vascularization of the intima never antedates the inception of the arteriosclerotic process, but is always its sequel.

In this connection it is essential to recall that the entire wall of the human pulmonary artery is well supplied with blood vessels,[41] yet arteriosclerosis of any extent in this artery in the absence of increased pulmonary arterial pressure[48, 49] or diabetes mellitus is exceedingly uncommon. Furthermore, although the walls of veins are richly supplied with capillaries throughout the various layers,[24, 41] the incidence and extent of phlebosclerosis are far overshadowed by sclerosis of the arterial tree. If the intramural circulation were basically at fault, one would certainly expect the reverse to be true. Goldblatt,[50] further, has made the pertinent comment that although anastomosing channels have been demonstrated within the intima of normal arteries of different animal species, the arteriosclerosis which occurs in such animals is usually medial in location, and quite different in character from that which is observed in man. Vascularization of the intima in man, then, under any circumstances, must be assumed to be the reaction—in a sense, perhaps, a nutritive and reparative one—to the arteriosclerotic degenera-

tive process. Its purpose is to furnish nourishment to a plaque which cannot rely for nutrition upon the process of imbibition alone, in the presence of intimal thickening. Once established, the capillary network unfortunately comes to form part of a vicious cycle through which the arteriosclerotic process is advanced, and may act as the decisive underlying factor in the subsequent occlusion of the main lumen, either by progressive fibrosis, extensive intramural hemorrhage, or thrombosis consequent upon dissolution or rupture of the plaque by hemorrhage.

ORIGIN OF INTRAMURAL VASCULAR TREE

The question as to the point of origin of the intramural vascular tree in arteriosclerosis is a rather difficult one to settle.

In many arteriosclerotic arteries that we examined it was a simple matter to decide that the majority of the large-calibered cross sections of the capillaries which were present were situated at the base of the plaque, i.e., toward the adventitia—notably where the plaque was fibrotic in type. In a much smaller number we were able to trace the origin of intimal capillaries directly from the lumen. In some the derivation of vascularization of an artery could not be definitely ascertained because cross sections of similar calibers were dispersed throughout the wall. In one or two instances capillary channels were seen in serial sections to traverse the entire thickness of the arterial wall. In most of the sections, however, it appeared that the more common source was the vasa vasorum, and not the main lumen of the artery. A similar belief has been expressed by others.[30, 31, 51, 35]

Leary[16, 47] has intimated that, in the young, the new mural capillaries may arise from the lumen, whereas in older persons the new channels usually stem from the vasa vasorum. We have not encountered this age variation in intramural capillary origin. Our histologic sections indicated that the vessels are derived from either the main lumen or the vasa vasorum, that the latter act as the main source, and that there is no relationship to the age of the subject.

There is a third possible source for capillaries within the walls of sclerotic arteries. Hueck[52, 53] and, later, Klemperer and Otani,[20] and, again, Klemperer[54] have presented evidence that embryonal mesenchyme, by virtue of its inherent developmental ability, may differentiate into hematic, phagocytic (histiocytic), endothelial, and fibroblastic cells. Hueck maintained that the arterial intima retains, even in postembryonic life, its basic mesenchymal potentialities. It is, further, well recognized that in arteriosclerosis a mesenchyme-like reticulum may be engendered by the degenerative process. When this has occurred, lymphocytes, mesenchymal cells, and, occasionally, polymorphonuclear leucocytes can be demonstrated within the altered intimal layer. It becomes anatomically conceivable, therefore, in view of the multiple potentialities of mesenchymal differentiation, that endothelialized vascular channels may arise through the stimulation to mesenchymal proliferation by the arteriosclerotic process.

INTRAMURAL HEMORRHAGE

Commonly associated with degenerating foci within sclerotic arteries, areas of recent hemorrhage and deposits of iron pigment have been noted; the latter are generally situated within the cytoplasm of macrophages. Intramural arterial hemorrhage has been observed repeatedly,[55, 56, 57, 58, 59, 60, 61] and its importance has been recently emphasized by Leary, Paterson, Winternitz and his associates, and Wartman. Benson[58] mentioned the occurrence of breaks in the intima, with hemorrhage into the wall. He thought that these hemorrhagic foci were derived from the lumen through breaks in the intima, and that they dissect the wall, and believed that these changes may lead to occlusion of the lumen, either by pressure or by thrombus formation. Koch and Kong expressed the similar opinion that blood masses entered the atheroma at the site of thrombosis. Boyd,[59] however, observed intimal hemorrhage and thrombosis of the arterial lumen, and implied that the hemorrhage was caused by injury of the intramural capillaries by an "inflammatory" exudate, and stated that thrombosis may result from such changes. Clark and his co-workers[61] described the "occurrence of a fresh break in the fibrous lining of a lipoid plaque, with penetration of blood elements into the area." Leary considered the entrance of blood into the arterial intima as secondary to a defect produced by rupture of an atheromatous "abscess."

Paterson,[32, 33, 34] to whom much credit is due for first emphasizing the etiologic relationship between intramural hemorrhage and thrombosis of the main lumen, pointed out that intimal hemorrhage is caused by rupture of capillaries which he believes have originated from the artery lumen. Such rupture was assumed to be dependent upon the association of high intracapillary pressure and atheromatous softening. The resultant intimal hemorrhage might act as the precipitating factor in coronary thrombosis. In a recent report, Paterson[34] expressed the belief that rupture of a capillary wall "may initiate thrombosis of a coronary artery by diffusion of blood from an intimal hemorrhage into the lumen, by necrosis or erosion of the intima from damage to its capillary circulation, or by retrograde thrombosis." Wartman[62] stressed the clinicopathologic significance of extensive intramural hemorrhage in arteriosclerotic vessels—the so-called hematomata—as a cause of acute arterial occlusion without the formation of a thrombus. Winternitz and his associates,[43, 41] more recently, have described in great detail the characteristics of mural vascularization and hemorrhage, and pointed out the importance of the role of hemorrhage in the development of arteriosclerosis.

We have been able to corroborate the findings of these authors, and feel, as Paterson, Wartman, and Winternitz and his co-workers have maintained, that in many instances hemorrhage may act as the precipitating cause of coronary thrombosis, either by actually producing dissolution and rupture of the plaque, with secondary thrombus formation, or by

inducing edematous transformation or degeneration in the intima overlying the hemorrhage, with subsequent involvement of the surface endothelium and thrombosis.

In our studies, hemorrhage into the walls of sclerotic arteries was observed with great frequency (Fig. 2). Such hemorrhages were commonly multiple, and were irregularly scattered through various portions of the arterial tree. We believe, with Paterson, that the hemorrhagic foci within the walls of sclerotic arteries arise within the wall, and are not derived from the lumen. In other words, intramural hemorrhage is not the result of thrombosis, but is rather its cause. This contention is substantiated by the very common occurrence of intramural hemorrhages in sclerotic plaques without any associated thrombus formation, and the ease with which capillaries from which such hemorrhages originate can be demonstrated. It is noteworthy that when a hemorrhagic focus was observed in this series, we could always demonstrate a coexistent zone of severe intimal degeneration.

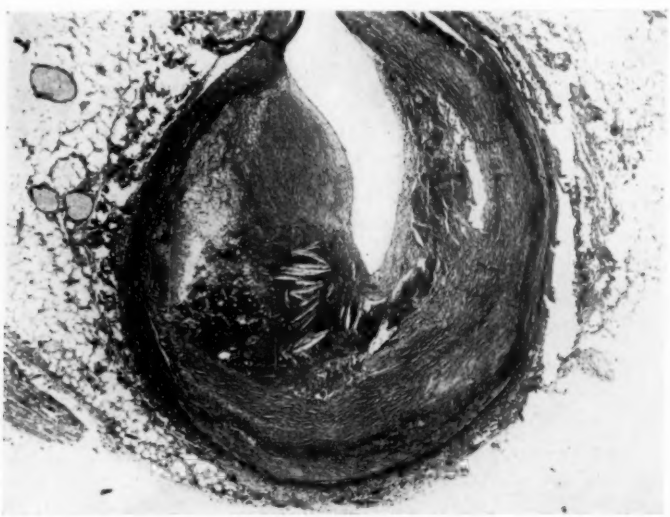

Fig. 2.—Low power photomicrograph shows hemorrhage into the degenerating fat plaque of the intima.

Relation Between Blood Pressure Level and Intramural Hemorrhage.—In view of the existence of intimal vascular channels within arteriosclerotic arteries, some of which communicate with the main coronary lumen, it is important to ascertain what relationship there is, if any, between intramural hemorrhage and the blood pressure level. That insufficiency of coronary artery blood flow, without actual thrombosis, may lead to extensive morphologic myocardial damage is well known.[63, 64, 65, 66, 67, 68] However, it is noteworthy that, in the instances reported in the literature, hemorrhage into coronary artery plaques was not mentioned, and, in the cases studied by one of us, with Friedberg,[68]

hemorrhages were entirely absent. It is remarkable that examination of the arteries in such cases occasionally revealed extensive intramural vascularization and associated arteriosclerosis, but no hemorrhagic foci. Further, in Moon's observations on shock,[69] although there was evidence of myocardial degeneration which was attributed to anoxemia, hemorrhages into vascular walls were not mentioned.

We believe, therefore, with Winternitz and his associates,[41] that when an insufficiency of intramural capillary blood flow exists, it is the result of compression of the delicate channels by the exudation, transudation, and progressive fibrosis which occur in a plaque, or of thrombosis of the capillary channel. Such interference with capillary blood flow may lead secondarily to necrosis, or perhaps to hemorrhagic "infarction" of its zone of supply. In our opinion, moreover, such a mechanism is operative only in the presence of moderately advanced arteriosclerosis.

It would appear, then, that decreased coronary artery blood pressure plays no role in the production of recent hemorrhage within the walls of arteries. The question might be raised whether or not an increased blood pressure has any part in such a process. Since intimal capillaries may arise directly from the main lumen, Paterson[32] has maintained that they are constantly exposed to a relatively high pressure, and, therefore, that a sudden increase in coronary artery pressure may rupture a capillary, with the production of local hemorrhage and, possibly, secondary thrombosis. Although sudden rises in coronary artery pressure may conceivably disrupt capillary channels which arise from the arterial intima, it is well known that not only marked fluctuations in the blood pressure, but also excessive pressures in patients with hypertension occur much more frequently than coronary artery occlusion. If this mechanism were significant, therefore, one would expect a much greater incidence of coronary artery occlusion in cases of hypertension, and any extreme fluctuation of blood pressure would then necessarily be attended by more disastrous results. Consequently we are not in accord with the contention that a sudden increase in blood pressure, in itself, is an important factor in producing intramural arterial hemorrhage. It appears to us that of the two factors which Paterson has stressed in the pathogenesis of arterial thrombosis, namely, intimal hemorrhage and plaque degeneration, the latter appears to be of greater significance. A zone of degeneration adjacent to a capillary may, in itself, effect rhexis of the capillary wall.

INTRAMURAL "FIBRINOID" SUBSTANCE

A "fibrinoid" substance was commonly associated with intramural hemorrhage. The nature, source, and significance of the so-called fibrinoid matter within arteriosclerotic plaques is still open to controversy. Does it originate extramurally from the vascular lumen, or does it arise within the wall? Does it play an important role in the arteriosclerotic process, or is it merely an adventitious substance? Mallory[57, 70]

noted the presence of fibrin-like material within the plaques in arteriosclerotic and syphilitic aortitis and believed that this substance represented degenerated or necrotic fibrous tissue. Jaeger[71] described fibrinoid masses which were both deposited upon, and situated within, arteriosclerotic plaques. The former he regarded as derived from the blood stream, whereas the latter were believed to be caused by necrosis of fibrous tissue. Leary[16] reported the occurrence of "fibrinous and fibrinoid necrosis" within the fibrous tissue of intimal plaques, with extension to the endothelial layer, and ascribed this change to a diminution of nutrition caused by growth of the plaque. Jucker[19] thought that either degeneration of collagenous substance on which precipitation of fibrinogen occurred, or loosening of the fibrillar substance, with penetration of plasma and secondary coagulation, accounted for such deposits. More recently, Clark and his associates[61] expressed the view that the fibrinoid masses situated on the surface of, and within, the plaques represent compressed and hyalinized blood elements, and that "in most instances (they) are the remnants of an organizing surface deposit." They also suggested that when ulceration of endothelium has occurred, the deeper layers represent coagulated blood plasma which has penetrated the plaque from the lumen of the vessel.

In a number of instances in which the "fibrinoid" material was found, we also noted erythrocytes in various stages of conglutination and degeneration, and frequently the conglutination was so advanced that the material appeared to be "fibrinoid," but with higher magnification the shadows of erythrocytes could be seen. Silver-impregnated fibers were found not only within the fibrinoid zones, but also within the adjoining tissue. These we felt were disrupted elastic fibrils. The Lepehne stain for hemoglobin was uniformly negative, although erythrocytes in the vicinity showed a decidedly positive reaction. Similarly, the Weigert fibrin stain gave negative results, although the specificity of this stain is questionable. Our anatomic observations have led us to believe, despite the negative results with the Weigert and Lepehne stains, that the substance in question represents blood elements which are so degenerated and chemically transformed that they can no longer be morphologically demonstrated as such with these stains.

In view of the rich intramural capillary network, we do not believe that infiltration of blood from the main arterial lumen plays an important part in such formations. Where intimal endothelial rupture has occurred, some slight infiltration may presumably occur. However, we do not think that this mechanism is significant, but are rather of the opinion that local rupture of capillaries within arteriosclerotic plaques provides the source of blood and "fibrinoid" material in the majority of instances. In a few cases, the fibrinoid material was found in zones in which there was no evidence of either recent or old hemorrhage within the plaque. Whether or not this represented extravasated blood

plasma could not be ascertained with any degree of certainty. We look upon the presence of "fibrinoid" material within the arterial wall as an incident in the degenerative cycle of arteriosclerosis—the result of extravasation of blood from the intramural capillary channels.

LATER SEQUELAE OF ARTERIOSCLEROSIS

Calcified plaques were commonly observed in the present series. The calcium deposits exhibited a predilection for the basal segments of the intima, but occasionally extended throughout the thickness of the intima and impinged upon the endothelium. The vascularization of the arterial wall in the vicinity of the calcified portion was usually sparse—a point previously emphasized by Paterson—and was most often noted along the lateral aspects of the plaque, less often at the base, and only rarely toward the lumen.

Bone formation within the intima was found in five cases, usually in the basal portions of the intima, and always within areas which were the seat of severe arteriosclerotic alterations. In four of these the bone trabeculae were associated with calcific fragments, and a gradual transition from calcium deposit to fully developed bone could be demonstrated, in one instance even with marrow formation and hematopoietic tissue. In the fifth case the bone had apparently completely replaced the calcium. In one instance, erosion of a capillary wall, presumably by a projecting spur of newly formed bone, had occurred, with the production of a focal area of intimal hemorrhage. In the popliteal artery of a lower extremity of a diabetic, amputated because of gangrene, we recently observed erosion of intima and endothelium by a bony plaque, with superimposition of an early parietal thrombosis. These observations indicate that the presence of bony plaques within arteriosclerotic arteries may precipitate acute changes within the arterial wall by producing erosion of vascular channels.

That bone may form within arteriosclerotic plaques is well known. Descriptions of its occurrence, however, have been confined, in the main, to the arteries of the extremities, the aorta, and the cardiac valves. Rohmer[72] and Moenckeberg[73] reported that the incidence of bone formation within senile arteriosclerotic plaques of the arteries of the extremities was as high as 10 per cent. These authors, as well as Jores,[13] looked upon its formation as evidence of metaplasia, and expressed the opinion that the new bone is usually derived from connective tissue in the vicinity, and always occurred following calcium deposition. Judging from our observations, bone formation is decidedly less common within the coronary arteries than in peripheral arteries. Search for it should be made in those vessels which exhibit extensive calcification grossly. When the stage of calcification and metaplasia into bone has occurred, the healing process may be considered to have reached its end point, and the capillaries supplying the area then become occluded and disappear.

Another frequent accompaniment of arteriosclerosis is medial atrophy, which appears to be directly proportional to the thickness of the adjacent plaque, and is, in a sense, therefore, a pressure atrophy. In several instances the atrophy was so advanced that the media could no longer be identified. This was particularly true in the vicinity of calcified and bony plaques. Leary,[15] however, has referred to the frequent occurrence of medial hypertrophy. Medial necrosis in arteriosclerosis has been reported by Feyrter,[74] but was not observed in our series of cases.

MORPHOGENESIS OF ARTERIOSCLEROSIS

Judging from the recorded, and our own, anatomic observations, it appears that the process of arteriosclerosis consists primarily of an intimal lipoidosis and collagenous thickening, and, further, that the end result is intimal fibrosis brought about with the aid of capillary channels which proliferate in response to the fatty change and intimal thickening. The ingrowth of vessels into the plaque must be considered, then, as basically reparative and granulation tissue-like in nature. If the vascularization of a plaque does not keep pace with the lipoid change, or if the delicate intramural channels become obstructed in any of the ways previously mentioned, the ensuing circulatory deficiency leads to necrosis of the lipoid zone, and produces an atheromatous "abscess." This establishes the second phase of the vicious cycle, for the necrotic foci may now precipitate localized hemorrhages, with progression of the arteriosclerotic process, and, incidentally, occlusion of the lumen. The extent of the local hemorrhage is dependent upon the ratio of the size of the capillary affected to the degree of associated intimal degeneration. Finally, then, the lesion must be the expression of the interrelationship between fatty change, vascularity of the wall, and intimal necrosis. Calcification and bone formation characterize ultimate healing of the lesion.

DISTRIBUTION OF ACUTE OCCLUSIVE LESIONS

Although acute arterial occlusions occurred predominantly in the left coronary artery and its secondary divisions, we found, despite common belief, that the right coronary artery, not the anterior descending branch of the left coronary, was, of all single arteries, most often the seat of acute occlusion. For many years it has been thought that the anterior descending branch of the left coronary artery is the one most frequently involved in coronary artery thrombosis,[75, 76] and, consequently, that the anterior surface of the left ventricle is the most common site of infarction. In this connection, it must be pointed out that we have recorded separately the pathologic changes which were found within the main anterior descending branch of the left coronary artery, and those within the ramus primus division of the anterior descending branch. It is probable that previous observers have not done this, but have included both sites under occlusion of the anterior descending branch. In forty-six cases of fatal occlusion reported by Levine and

Brown,[77] the left anterior descending branch was occluded thirty-nine times, and the right coronary only twice. However, in our series (Table I) the right coronary artery was more often the seat of recent involvement—sixty-one instances—and recent infarction of the posterior wall of the left ventricle was correspondingly more common than that of the anterior wall. Next to the right circumflex artery, the largest number of recent occlusions occurred in the anterior descending branch of the left coronary artery (fifty-six instances). Twenty-seven and fifteen recent closures, respectively, were found within the circumflex branch of the left coronary and the primary divisions of the anterior descending branch of the left coronary. The incidence of recent changes in the remainder of the coronary tree is indicated in Table I. White[78] has stated that "The preponderance of involvement of the left anterior descending is not nearly as great as used to be believed; it is only slightly in the lead." We agree with Bork,[10] Barnes and Ball,[79] and Master and his associates[80] that the left anterior descending artery should no longer be referred to as "the artery of coronary occlusion."

In forty-eight of our one hundred seventy-two instances of acute arterial occlusion, two or more arteries were occluded simultaneously, an occurrence which has been emphasized by Saphir, et al.,[9] and others.[81, 82]

In three cases a single recent occlusion caused death in individuals in whom there was no evidence of previous myocardial infarction, and in whom arteriosclerosis of the coronary arteries was only moderate in degree. It is to be emphasized, however, that in the majority of cases of acute arterial occlusion we found that this event occurred in arteries which showed extensive sclerotic involvement, with associated narrowing of the lumina, and that the acute lesions were often multiple. In not a single instance was thrombosis found to have occurred within a normal artery. Clawson[5] has stated that thrombosis of a nonsclerotic vessel is rare. Others[83, 59, 46, 84] have denied that thrombosis of normal vessels ever occurs.

TABLE II

PATHOGENESIS OF ACUTE CORONARY OCCLUSION (100 POST-MORTEM CASES)

	LEFT CORONARY ARTERY						RIGHT CORONARY ARTERY			
	LAD	1°	LC	VSA	MO	VSP	RC	VDA	SLP	TOTAL
Thrombosis secondary to hemorrhage	15	2	7	0	1	0	27	0	1	53
Thrombosis related to hemorrhage	2	1	4	0	0	0	4	0	0	11
Hematoma of the wall	6	0	3	0	0	0	4	0	0	13
Hemorrhage into 4+ sclerotic artery	8	5	3	0	2	0	4	0	1	23
Thrombosis on a plaque	16	4	6	2	4	0	13	0	0	45
Nonoccluding parietal thrombosis on a plaque	3	3	1	0	0	0	1	0	0	8
Channel thrombosis	3	0	0	0	0	0	2	0	0	5
Thrombosis of undetermined pathogenesis	3	0	3	0	0	1	6	1	0	14
Total	56	15	27	2	7	1	61	1	2	172

VARIETIES OF RECENT OCCLUSIVE CHANGES (TABLE II)

We found fifty-three instances in which the coronary thrombosis was secondary to dissolution of an arteriosclerotic plaque subsequent to an intramural hemorrhage (Figs. 3 and 4). In the majority of these instances the components of the thrombus within the lumen were evidently of the same age as the hemorrhagic focus within the wall. In a small number, however, changes within the degenerated intimal focus, such as red cell degeneration, "fibrinoid" transformation, plasma mass compression, organization of fibrin, and formation of iron pigment, suggested either that there had been repeated, small hemorrhages before the final intimal disruption had occurred, or that a slow, progressive hemorrhage had preceded by at least a number of days the communication with the lumen and formation of a thrombus (Fig. 4). It is apparent, therefore, that arterial occlusion may be the result of a series of changes within the vessel wall, and that the development of the closure may be somewhat slow and progressive. Barnes[85] has previously suggested that coronary artery thrombosis may develop gradually, so that one to three days may elapse before complete occlusion occurs. Levy,[86] Clark, et al.,[61] and Paterson[34] have also alluded to such a possibility. In view of the evidence that the tempo of arterial occlusion may vary, it is conceivable that the progressive changes within the wall of the coronary artery may be the morphologic substratum of the premonitory symptoms of its final occlusion.

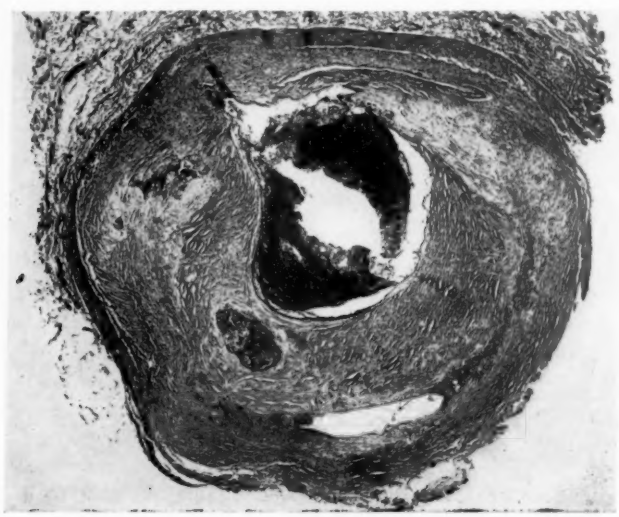

Fig. 3.—Low power photomicrograph of the section of the coronary artery showing foci of hemorrhage into the zones of intimal degeneration and thrombosis of the lumen. In this section there is no apparent association between intimal hemorrhage and thrombus formation.

Occasionally, when the degeneration is extensive—for example, in an atheromatous abscess—and impinges upon the subendothelial zone, we have found that very little hemorrhage is required to produce rupture

of the endothelial layer and to initiate secondary thrombus formation (Fig. 5). In one instance, in the same block of a coronary artery, we observed two points of simultaneous hemorrhage into such severely degenerated areas, with secondary rupture and communication with the lumen. In two instances the extension of an atheromatous abscess to the endothelial layer was presumably the cause of thrombus formation through the mechanism of direct endothelial injury.

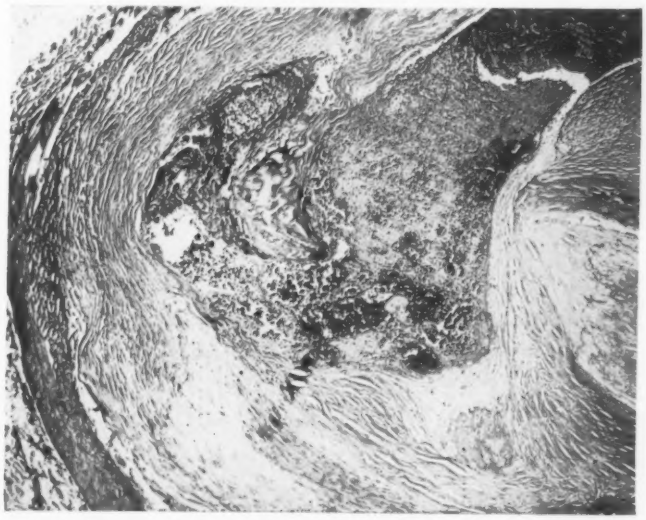

Fig. 4.—High power photomicrograph of serial section of the artery shown in Fig. 3, to show extension of the intimal hemorrhage and degeneration, with final dissolution of the intima and thrombotic occlusion of the lumen. Note the fibrinous character of the intimal lesion, indicating an origin antedating thrombosis.

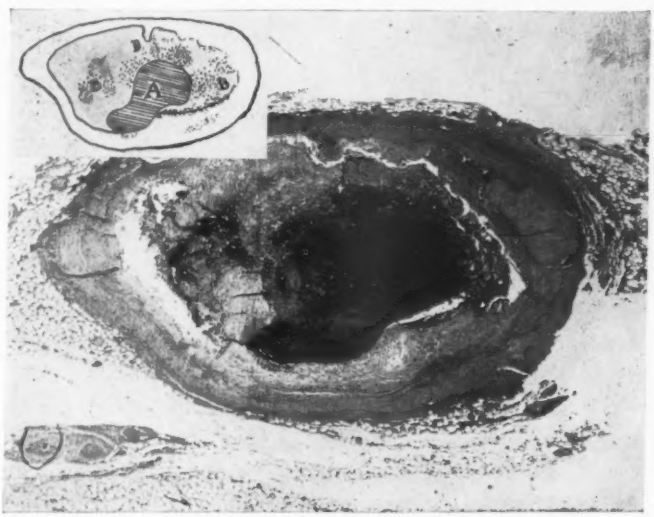

Fig. 5.—Low power photomicrograph shows multiple small foci of hemorrhage into the large atheromatous "abscess," with secondary thrombosis of the lumen. Diagram: *A*, lumen; *B*, foci of hemorrhage in "abscess."

In eleven cases thrombosis had occurred in an artery which was the seat of the hemorrhage, but the latter had not contributed directly to the formation of the thrombus, for we could not trace, in serial sections, any direct communication between the intramural hemorrhage and the occluding thrombus. Always coexistent with the focus of hemorrhage within the wall was either fatty degeneration, loose separation of the overlying intimal fibers, or a scattering of erythrocytes impinging upon the endothelial surface (Fig. 6). In our opinion, these changes were either originally induced, or intensified, by the hemorrhage, and were the basic cause for the ensuing endothelial damage and thrombus formation.

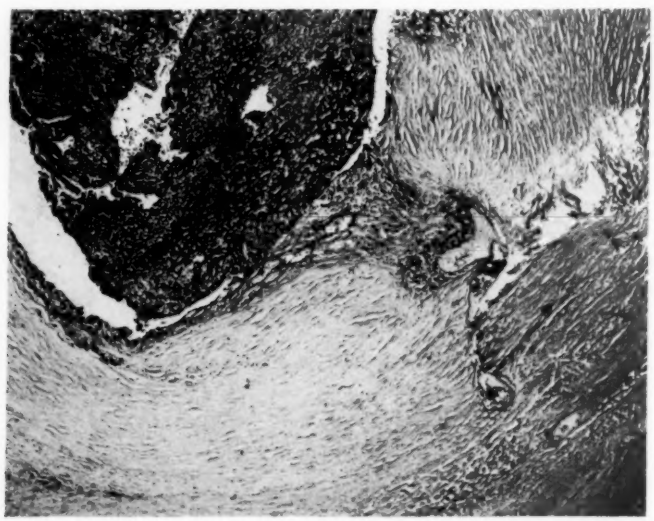

Fig. 6.—Medium power photomicrograph shows thrombus formation secondary to intimal hemorrhage and acute degenerative changes, without dissolution of the plaque. Note the capillary leading to the hemorrhagic focus.

Forty-five occluding thrombi of the coronary arteries had formed on a plaque which showed either a loose, edematous, fibrillar proliferation, lipoid infiltration, or intimal necrosis, i.e., "thrombosis on a plaque." In two of these, however, the intima showed no evidence of any recent change, but consisted merely of dense, fibrous tissue. In several of these, and also in a few instances in which thrombosis had occurred as a result of intramural hemorrhage, evidence of organization was found; in some it appeared that the recent change might have been superimposed from the lumen. There were thirteen cases of recent, extensive hemorrhage into a degenerating plaque, with occlusion of the lumen, but without thrombosis (Fig. 7). In these cases either the hemorrhage was so extensive, or the plaque so necrotic, that the sudden increase in intimal pressure caused by the hemorrhage was presumed to be sufficient to cause complete occlusion of the artery. In three cases, either recent myocardial infarction or sudden death was attributed to only

moderate hemorrhage into a markedly thickened plaque in a vessel with an extremely narrow lumen.

Two organizing hematomas were observed, and eight parietal, non-occluding thromboses on arteriosclerotic plaques. In two of the latter, early organization of a portion of the parietal thrombus had proceeded to such an extent that it appeared to be a thickened, arteriosclerotic plaque. This was a striking example of the fact that once organization has occurred it becomes impossible in most instances to ascertain whether or not there has been a previous thrombosis. In fourteen instances, the pathogenesis of the individual thrombus could not be satisfactorily determined, either because the block containing the thrombus was not available in its entirety for microscopic study, or because the morphogenesis was unclear. Five examples of intramural, channel thrombosis were observed in our series, although only two were considered to be clinically significant.

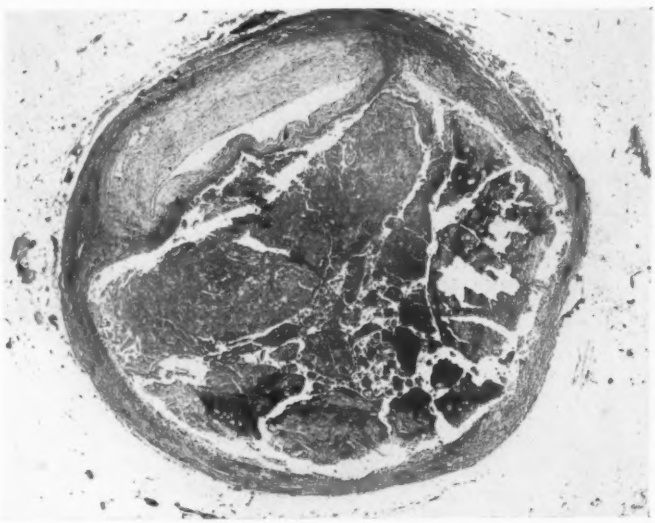

Fig. 7.—Low power photomicrograph shows hemorrhage into the large atheromatous abscess, with compression occlusion of the lumen.

The above figures indicate that the incidence of intramural hemorrhage, in our series, as a factor in coronary artery occlusion was 62.5 per cent, whereas thrombosis on an arteriosclerotic plaque occurred in 37.5 per cent. Statistical analysis shows, therefore, that intramural hemorrhage is the most frequent underlying mechanism in coronary artery occlusion.

We re-emphasize that, without exception, every artery which was the seat of either intramural hemorrhage or vascular thrombosis exhibited sclerotic change. However, although the majority of these recent changes was noted in arterial cross sections which showed well-marked arteriosclerosis, a small number of thromboses, usually secondary to hemor-

rhagic disruption of the wall, was found in portions of arteries which were the seat of only slight to moderate arteriosclerosis. This was particularly true of the right coronary artery. In several instances in which a thrombus had formed, there was an intimal reaction which consisted of collections of lymphocytes, polymorphonuclear leucocoytes, and, rarely, minute foci of hemorrhage which were usually immediately beneath the endothelium. It is noteworthy that, on examination of cross sections of thickened arteries which were not the seat of thrombosis, a similar subendothelial and initimal cellular infiltration, associated with a loose, edematous, fibrillar stroma, was found. Since these alterations were found under different circumstances, and often in the absence of thrombosis, we must assume that such reactive foci within the intima may precede the development of thrombi, and are reactive manifestations to arteriosclerotic intimal degeneration. In view of the fact that this change was noted in the absence of thrombosis, and, in almost every case of thrombosis on a plaque, we feel that it is of pathogenetic importance. It may be that changes of this type are responsible for the alteration in the physical properties of the endothelium which induces a local change in the current, as suggested by Dietrich and Schroeder,[87] and therefore, favor the formation of a thrombus. Klotz and Lloyd[46] have alluded to foci of "nodular endarteritis" as favoring the development of thrombosis. The presence of distinct, recent changes in the arterial wall in almost all instances of coronary occlusion, then, emphasizes the importance of the belief of Welch,[88] and others,[58, 13] that coronary artery thrombosis is merely an incident in the development of arteriosclerosis.

In the majority of instances in which a thrombus was found, unassociated with intimal hemorrhage, we could demonstrate its origin at a point in the arterial segment which disclosed the most advanced sclerotic changes and narrowing. In addition to occlusion of the lumen at this point, there was both proximal and distal propagation of the thrombus. We do not concur with Koch and Kong,[60] Clark and his co-workers,[61] and Paterson,[33] in their contention that stasis of coronary blood flow may be so pronounced as to induce the formation of a thrombus proximal to a zone of severe arterial stenosis. In all but two of our series of cases of thrombosis on a plaque, we noted a primary, recent, basic change within the subendothelial tissue that could account for secondary endothelial abnormalities which may favor thrombus formation. These changes were usually situated at the point of greatest narrowing. In the other two cases the thrombus occurred in an artery which was only moderately narrowed, and was not related to any severe, distal obstruction. We subscribe to the belief, therefore, that the intrinsic changes within the plaque are primarily responsible. However, the proximal propagation of the thrombus must be accomplished through the arrest of the circulation in the occluded portion of the arterial tree.

In summary, then, it is clear that coronary artery occlusion may be effected by dissolution of the intima by hemorrhage; by hemorrhage into an atheromatous "abscess," causing compression of the lumen; through the mechanism of recent intimal and endothelial changes brought about by a remote focus of hemorrhage; by endothelial injury resulting from the impingement of an atheromatous "abscess"; and, finally, by the formation of a thrombus on an arteriosclerotic intimal plaque.

There was no instance of embolic occlusion of the coronary arteries in this series, nor could we demonstrate in any case the occurrence of secondary coronary embolism from a more proximal plaque or thrombus within the artery.

DIFFERENTIATION OF PROGRESSIVE ARTERIOSCLEROSIS FROM PREVIOUS THROMBOTIC OCCLUSION OF LUMEN

The presence of severe intimal fibrosis, extensive medial atrophy, and even disappearance of the muscle layer, coupled with the elastic fragmentation, and the association with a prolific vascular response to the arteriosclerotic process have made it difficult to ascertain with any degree of certainty the pathogenesis of the severe narrowing of the lumina of the arteries. Moreover, the observed occurrence of similar processes, plus iron-pigment deposition secondary to intramural hemorrhage and progressive fibrosis, has nullified completely the value of these criteria which were supposedly of aid in differentiating thrombosis from the changes incident to progressive arteriosclerosis. Further, we have noted, in hearts which were the seat of large, old myocardial infarcts, arterial changes which were even less severe than in those in which no old myocardial infarcts were discovered. The occurrence of parietal thrombi, such as we have seen in this series and as others[4, 60, 6, 61] have observed, also leads to confusion, for when such a lesion is finally replaced by fibrous tissue and incorporated into the intima, the affected segment of the wall appears exactly like an area which has been progressively thickened by fibrosis of a zone of intimal lipoidosis. The vascularization that may occur here, as well as subsequent to extensive hemorrhage, is often so pronounced and diffuse that such vessels may become indistinguishable from the original lumen. It is common knowledge that new channel formation in an arteriosclerotic plaque may become so marked, and the vessels so enlarged, that the lesion resembles a recanalized thrombus. In a small number of instances we have observed that such vessels may develop elastic tissue. Von Glahn[51] has made a similar observation. Occasionally, we have seen the walls of these small blood channels become completely hyalinized.

Furthermore, our own observations, and those of others, on organizing hematomas lead us to believe that extensive hemorrhage into the wall of a coronary artery may produce virtual occlusion without communicating with the lumen. That complete re-establishment of the original caliber of the lumen as a result of replacement fibrosis and contraction

may occur is readily conceivable. In support of such a possibility is the not infrequent finding of an extensive, old, myocardial infarct without any narrowing of the coronary artery supplying this area. It is obvious that a resorbed and organized hematoma, therefore, could not be differentiated from even a small "arterioselerotic" plaque. Neither could the presence of iron pigment be used as a histologic criterion for the diagnosis of a previous coronary thrombosis, for we now know that the deposition of such pigment is most often the result of focal intramural hemorrhage, without thrombus formation. Nor does the absence of iron pigment within an arterioselerotic plaque negate the possibility of previous hemorrhage, for macrophagic activity is very pronounced after hemorrhage has occurred within the wall, and the blood pigments may be completely removed. We have noted iron-laden macrophages traversing the entire thickness of portions of the wall of an artery which had been the seat of relatively recent hemorrhage, and even situated within the periadventitial tissue. Fragmentation of elastic lamellae is also of no aid in ascertaining the anatomic history of a zone of marked arterial thickening, for, as the aging process advances, splitting of the intimal elastic membrane is common,[8, 30] and its disruption by intramural hemorrhage, without occlusion, further confuses the picture.

When this study was begun, we believed that a previous thrombotic occlusion could be differentiated in most instances from the lesion produced by a slow, progressive type of arterioselerotic thickening. However, when the significance of the above-mentioned changes was fully realized, restudy of our early slides proved that our original impressions were erroneous, and we felt that the only correct evaluation of the old arterial lesions would be merely to indicate the extent and degree of sclerotic change. Only when we encountered an organized myocardial infarct supplied by an artery which exhibited pronounced plaque formation, with associated narrowing of the lumen and distortion of the mural layers, could we postulate the occurrence of a previous acute coronary occlusion.

It must be mentioned, however, that a microscopic diagnosis of previous thrombotic occlusion is occasionally justified when evidence of disruption of the intimal layer by hemorrhagic extravasation can be obtained. This should be based on the finding of rich granulation tissue extending in "mushroom" fashion through the intima, with the head of the "mushroom" occupying what is assumed to be the former site of the coronary lumen.

Benson[58] and Winternitz and his co-workers[41] voiced a similar opinion. The latter authors stated "that when a vessel is finally completely occluded with granulation tissue, the events leading to the occlusion cannot be reconstructed with any degree of certainty."

Perivascular Lymphocytic Infiltration.—A frequent accompaniment of arteriosclerosis was the infiltration of the periadventitial and ad-

ventitial tissue with small lymphocytes, often about proliferating blood vessels (vasa vasorum) (Fig. 8). It is important to recognize the frequency of such an infiltration, particularly in severely sclerotic arteries, for medial fibrosis and vascularization are associated with such an infiltration, so that it is possible to confuse such alterations with the lesions of syphilis. In view of the common occurrence of this process in arteriosclerotic vessels, we believe that the diagnosis of syphilis of the coronary arteries should be entertained only when a well-marked obliterating endarteritis is found within the adventitial vessels in association with such lymphocytic proliferations.

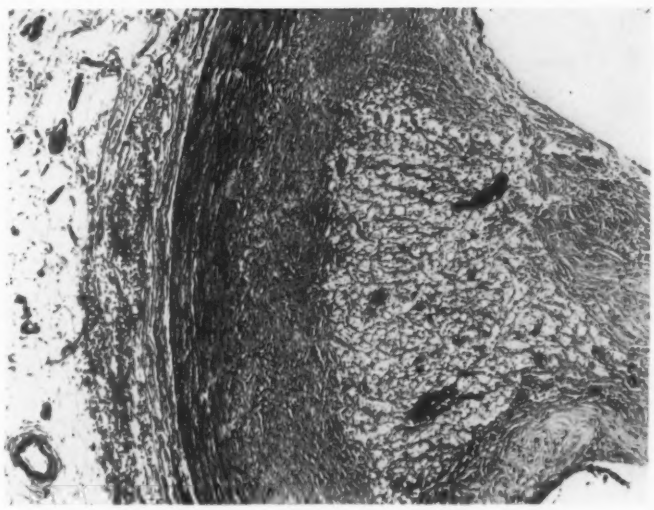

Fig. 8.—Medium power photomicrograph shows marked adventitial lymphocytic infiltration in arteriosclerosis. Note the capillaries interspersed in the lipoid intimal plaque.

Syphilis of the Coronary Arteries.—In the four instances of syphilitic aortitis which were included in our series, sections taken from various segments of the coronary arteries, including those segments immediately distal to the ostia, did not reveal evidences of syphilis, but merely disclosed the presence of arteriosclerosis. True syphilitic involvement of the coronary arteries is usually an extension from the aorta, with the not infrequent sequel of ostial stenosis, whereas involvement of the arteries beyond their origin is of little significance.[89] Although ostial narrowing caused by syphilitic involvement of the coronary arteries was found in thirty-seven of 107 cases studied by Saphir and Scott,[25] syphilis could not be demonstrated within the stems of the vessels.

Aneurysm of the Coronary Arteries.—In order to cover our observations fully, we mention briefly the subject of coronary artery aneurysm. Aneurysm of the coronary arteries, especially when compared with the incidence of arteriosclerosis of those vessels, is a distinct rarity.

Only one saccular aneurysm was encountered in our series of cases; it involved the right coronary artery, and was associated with an extensive, recent, dissecting hemorrhage immediately bordering its distal limit. This is particularly significant when considered in the light of the role which has been ascribed to hemorrhage in the production of arterial changes. In view of the extent and site of the hemorrhage, it is logical to assume that the aneurysm had resulted from previous hemorrhagic dissection of the wall of the coronary artery. That this is the pathogenesis of dissecting arterial aneurysm has been suggested previously.[55, 56, 40] For a fuller discussion of this subject the reader is referred to the papers of Packard and Wechsler[90] and Chiari.[91]

SUMMARY AND CONCLUSIONS

1. The results of a study of 100 cases of recent coronary occlusion and a review of the pertinent literature are presented. Particular attention, with the aid of serial sections of the arteries, was paid to the relative importance of intimal hemorrhage and primary thrombosis on an arteriosclerotic plaque in the pathogenesis of acute coronary occlusion, and also to the relationship between the extent of vascularization, hemorrhage, and intimal sclerosis.

2. The main branches of the coronary arterial tree exhibited advanced sclerotic changes with approximately equal frequency, although the incidence in the anterior descending branch of the left coronary artery was perhaps slightly higher than elsewhere.

3. The intermuscular branches of the coronary arteries exhibited arteriosclerotic changes only rarely.

4. Vascularization of the intima was found only in the presence of arteriosclerosis, and was regarded as a sequel, not the basic cause, of the intimal degenerative changes. Once established, however, vascularization may be an important factor in the further advance of the arteriosclerotic process. The extent and degree of atheromatous "abscess" formation in the intima are usually in inverse ratio to the vascularization.

5. Intramural hemorrhage was observed frequently, and was always found to be associated with vascularization and plaque degeneration. It is our belief that it originated invariably within the wall, rather than by imbibition from the lumen.

6. Coronary artery occlusion may be produced either by intramural hemorrhage (62.5 per cent), or by the formation of a thrombus on an arteriosclerotic plaque (37.5 per cent).

7. Intramural hemorrhage was found to lead to coronary artery occlusion either by inducing acute degenerative and reactive responses in the plaque overlying the hemorrhage, by obstructing the artery mechanically, or by actually producing dissolution and rupture of the intimal layer. The extent and variety of change are dependent upon the relationship between the vascularity of the plaque and the degree of degeneration therein.

8. Occlusion of a coronary artery produced by the deposition of a thrombus on a plaque is usually secondary to an edematous, acute, reactive or degenerative change in the subendothelial tissue.

9. The coexistence of recent and organizing changes within a plaque or its thrombus supports the belief that coronary artery occlusion may be a slow, progressive process.

10. Contrary to common belief, the individual artery most frequently the seat of acute occlusion was the right coronary artery. Simultaneous, multiple occlusions of the coronary arteries were common.

11. Fibrinoid-like masses within arteriosclerotic plaques were considered to be the sequelae of intramural hemorrhages or extravasated blood plasma originating from the mural capillaries within the plaque.

12. Calcification was found frequently within degenerating plaques. Bone formation was noted in five cases. Vascularization in these foci was usually sparse.

13. Distortion of the architecture of the wall produced by slow, progressive arteriosclerosis and repeated hemorrhage, with reactive vascular proliferation, nullifies the value of criteria used to differentiate arteriosclerotic narrowing from previous thrombotic occlusion. In the majority of cases the only correct pathogenetic evaluation of the old arterial lesions is a statement of the extent and degree of arteriosclerotic change.

14. A prominent, adventitial, perivascular infiltration of lymphocytes was often encountered in arteriosclerotic vessels.

15. Medial atrophy was frequent and appeared to be in direct proportion to the intimal thickening.

16. Aneurysm of the right coronary artery was observed once. This had been produced by a hemorrhagic dissection of the wall.

17. Arteriosclerosis was observed in every instance in which either a partial or complete arterial occlusion was found. In not a single instance had a thrombus developed within a normal artery.

18. Judging from this morphologic analysis, coronary artery occlusion is an incident in arteriosclerosis. The direct, immediate, precipitating factors underlying recent occlusive changes could not be ascertained in this survey.

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REFERENCES

1. Master, A. M., Horn, H., Dack, S., Jaffe, H. L., and Finkelstein, L. E.: The Pathology of Coronary Artery Occlusion and Myocardial Infarction, etc. Read before the Am. Heart Assoc. St. Louis. May, 1939. To be published.
2. Spalteholz, W.: Die Arterien der Herzwand, Leipzig, 1924, S. Hirzel.
3. Gross, L.: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber.
4. Wolkoff, K.: Ueber die Atherosclerose der Coronararterien des Herzens, Beitr. z. path. Anat. u. z. allg. Path. **82:** 555, 1929.
5. Clawson, B. J.: Coronary Sclerosis, Am. Heart J. **17:** 387, 1939.
6. Karsner, H. T.: Coronary Arteriosclerosis, in Arteriosclerosis: A Survey of the Problem, Ed. E. J. Cowdry, New York, 1933, The Macmillan Co.

7. Kutschera-Aichbergen, H.: Ueber die pathologische Anatomie der Angina pectoris, Wien. klin. Wchnschr. **41:** 6, 1928.
8. Wolkoff, K.: Ueber die histologische Struktur der Coronararterien des menschlichen Herzens, Virchows Arch. f. path. Anat. u. Physiol. **241:** 42, 1923.
9. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am. Heart J. **10:** 567, 762, 1935.
10. Bork, K.: Ueber Kranzadersklerose, Virchows Arch. f. path. Anat. **262:** 646, 1926.
11. Glomset, D. J.: Atherosclerosis of the Coronary Arteries, Arch. Path. **26:** 411, 1938.
12. Sutton, D. C., and Brandes, W. W.: Arteriosclerosis of the Coronary Arteries: Clinical-Pathological Study, J. Lab. and Clin. Med. **16:** 1185, 1930.
13. Jores, L., in Henke, F., and Lubarsch, O.: Handbuch der Speziellen Pathologischen Anatomie und Histologie. Vol. 2. Herz und Gefaesse, Berlin, 1924, Julius Springer.
14. Lange, F.: Studien zur Pathologie der Arterien insbesondere zur Lehre von der Arteriosclerose, Virchows Arch. f. path. Anat. u. Physiol. **248:** 463, 1924.
15. Leary, T.: Pathology of Coronary Sclerosis, Am. Heart J. **10:** 328, 1935.
16. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis, Arch. Path. **17:** 453, 1934.
17. Leary, T.: Atherosclerosis—Special Consideration of Aortic Lesions, Arch. Path. **21:** 419, 1936.
18. Bruening, F.: Die Ernährung der Gefässwand, Klin. Wchnschr. 3: 2282, 1924 (cited by Ramsey).
19. Jucker, P.: Ueber die Nekrose in der arteriosclerotischen Platte und ihre Beziehung zum Atherom, Virchows Arch. f. path. Anat. **295:** 301, 1935.
20. Klemperer, P., and Otani, S.: "Malignant Nephrosclerosis" (Fahr), Arch. Path. **11:** 60, 1931.
21. Risse, A.: Observationes quaddom de arteriorum statu normali atque pathologico, Inorg. Dis. Regiomonti, Pr. E. J. Dolkonski, 1853 (cited by Ramsey).
22. Klotz, O.: Concerning Compensatory Hyperplasia of the Intima, J. Exper. Med. **12:** 707, 1910.
23. Martin, H.: Recherches sur la pathogénie des lésions athéromateuses des artères. Rev. de méd. Paris **1:** 35, 1881 (cited by Kaufmann).
24. Gimbert, J. L.: Structure et texture des Artères, Thèse No. 81. Paris, 1865 (cited by Ramsey).
25. Saphir, O., and Scott, R. W.: Observations on 107 Cases of Syphilitic Aortic Insufficiency with Special Reference to the Aortic Valve Area, the Myocardium and Branches of the Aorta, Am. Heart J. **6:** 56, 1930.
26. Zahn, F. W.: Ueber Vascularisation der Media und Intima bei Endarteritis chronica, Verhandl. d. X internat. med. Cong. 1890, Berl. 3: 123, 1891 (cited by Ramsey).
27. Aschoff, L.: Arteriosclerose, Beihefte z. med. Klinik. **10:** Part I, 1914.
28. Letierce, E. E.: Essai sur quelques points d'anatomie et de physiologie médicale et surgicale de la membrane interne des artères, Thèse de la Faculté de Méd. de Paris, No. 218, 1829 (cited by Leary).
29. Marchand: Real-Enzyklopädie der gesammten Heilkunde von Albertus Eulenberg hrsg. z. Aufl. Wien und Leipzig, 1885. Cop. "Arterien" **1:** 687 (cited by Ramsey).
30. Gross, L., Epstein, E. Z., and Kugel, M. A.: Histology of the Coronary Arteries and Their Branches in the Human Heart, Am. J. Path. **10:** 253, 1934.
31. Kaufmann, E.: Pathology for Students and Practitioners, Translated by S. P. Reimann, Vol. 1. Philadelphia, 1929, P. Blakiston's Son and Co.
32. Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, Arch. Path. **22:** 313, 1936.
33. Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as Causative Factor in Coronary Thrombosis, Arch. Path. **25:** 474, 1938.
34. Paterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombi, J. A. M. A. **112:** 895, 1939.
35. Koester, K.: Ueber die Structure der Gefaesswaende und die Entzuendung der Venen, Sitzungsber. der mederrh. gesellsch. f. natur und Heilkunde Bonn. **32:** 128, 1875 (cited by Ramsey).
36. Koester, K.: Ueber Endarteritis und Arteritis, Berlin. klin. Wchnschr. **13:** 454, 1876.
37. Klotz, O.: Arterial Lesions Associated with Rheumatic Fever, J. Path. and Bact. **18:** 259, 1913.

38. Sewell, W. T.: Some Observations on the Pathology of Arterial Disease, Univ. of Durham, College of Med. Gaz. **14**: 25, 1913 (cited by Ramsey).
39. Robertson, J. F.: Vascularization of the Thoracic Aorta, Arch. Path. **8**: 881, 1929.
40. Tyson, M. O.: Dissecting Aneurysms, Am. J. Path. **7**: 581, 1931.
41. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Baltimore, 1938, Charles C. Thomas.
42. Ramsey, E. M.: Nutrition of the Blood Vessel Wall; Review of the Literature, Yale J. Biol. and Med. **9**: 13, 1936.
43. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: Studies in the Pathology of Vascular Disease, AM. HEART J. **14**: 399, 1937.
44. Aschoff, L.: Lectures on Pathology, New York, 1924, Paul B. Hoeber, Inc.
45. Ehrich, W., de la Chapelle, C., and Cohen, A. E.: Anatomical Ontogeny. B. Man. I. A Study of the Coronary Arteries, Am. J. Anat. **49**: 241, 1931.
46. Klotz, O., and Lloyd, W.: Sclerosis and Occlusion of the Coronary Arteries, Tr. A. Am. Physicians. **45**: 108, 1930.
47. Leary, T.: Vascularization of Atherosclerotic Lesions, AM. HEART J. **16**: 549, 1938.
48. Moschcowitz, E.: The Cause of Arteriosclerosis, Am. J. M. Sci. **178**: 244, 1929.
49. Moschcowitz, E.: Arteriosclerosis: The Cyclopedia of Medicine **3**: 211, 1932, F. A. Davis Co.
50. Goldblatt, H.: Book Review: Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, AM. HEART J. **46**: 765, 1938.
51. Von Glahn, W. C.: The Pathology of the Coronary Arteries in Diseases of the Coronary Arteries and Cardiac Pain, Ed. R. L. Levy, New York, 1936, The Macmillan Co.
52. Hueck, W.: Anatomisches zur Frage nach Wesen und Ursache der Arteriosclerose, München. med. Wchnschr. **67**: 535, 1920 (cited by Klemperer and Otani).
53. Hueck, W.: Ueber das Mesenchym, Beitr. z. path. Anat. u. z. allg. Path. **66**: 330, 1920 (cited by Klemperer and Otani).
54. Klemperer, P.: The Relationship of the Reticulum to Diseases of the Hematopoietic System; In Contributions to the Medical Sciences in honor of Dr. Emanuel Libman by his Pupils, Friends and Colleagues **2**: 655, 1932, International Press.
55. Babes, V., and Mironescu, T.: Ueber dissezierende Arteritis und Aneurysma dissecans, Beitr. z. path. Anat. u. z. allg. Path. **48**: 221, 1910 (cited by Tyson).
56. Moriani, G.: Ueber einen Fall von Aneurysma dissecans aortae mit besonderer Beruecksichtigung der frischer Rupturen der Aortenmedia, Virchows Arch. f. path. Anat. **202**: 283, 1910.
57. Mallory, F. B.: The Principles of Pathologic Histology, Philadelphia, 1914, p. 445, W. B. Saunders and Co.
58. Benson, R. L.: The Present Status of Coronary Arterial Disease, Arch. Path. **2**: 876, 1926.
59. Boyd, A. N.: An Inflammatory Basis for Coronary Thrombosis, Am. J. Path. **4**: 159, 1928.
60. Koch, W., and Kong, L. C.: Ueber die Formen des Coronarverschlusses die Aenderungen im Coronarkreislauf und die Beziehungen zur Angina pectoris, Beitr. z. path. Anat. u. z. allg. Path. **90**: 21, 1932.
61. Clark, E., Graef, I., and Chasis, H.: Thrombosis of the Aorta and Coronary Arteries: With Special Reference to the "Fibrinoid" Lesions, Arch. Path. **22**: 183, 1936.
62. Wartman, W. B.: Occlusion of Coronary Arteries by Hemorrhage into Their Walls, AM. HEART J. **15**: 459, 1938.
63. Libman, E.: The Importance of Blood Examinations in the Recognition of Thrombosis of the Coronary Arteries and Its Sequelae, AM. HEART J. **1**: 121, 1925; **10**: 399, 1935.
64. Obendorfer: Die anatomischen Grundlagen der Angina pectoris, München med. Wchnschr. **72**: 1495, 1925.
65. Büchner, F., Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz, Leipzig, 1935, Georg Thieme.
66. Levy, R. L., and Bruenn, H. G.: Acute Fatal Coronary Insufficiency, J. A. M. A. **106**: 1080, 1936.
67. Bean, W. B.: Infarction of the Heart. III. Clinical Course and Morphological Findings, Ann. Int. Med. **12**: 71 1938.
68. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**: 1675, 1939.

69. Moon, V.: Shock: A Definition and Differentiation, Arch. Path. **22**: 325, 1936.
70. Mallory, F. B.: The Infectious Lesions of Blood Vessels, Harvey Lectures 1912-1913, Philadelphia, 1913, p. 150, J. B. Lippincott Co.
71. Jaeger, E.: Zur pathologischen Anatomie der Thrombangiitis obliterans bei Juveniler, Virchows Arch. f. path. Anat. **284**: 526, 584, 1932.
72. Rohmer, P.: Ueber Knochenbildung in verkalkten endocarditischen und endarteritischen Herden. Virchows Arch. f. path. Anat. u. Physiol. **166**: 13, 1901.
73. Moenckeberg, J. G.: Ueber Knochenbildung in der Arterienwand, Virchows Arch. f. path. Anat. u. Physiol. **167**: 191, 1902.
74. Feyrter, F.: Ein eigenartiger Fall von Myomalacia Cordis, Frankfurt. Ztschr. f. Path. **33**: 1, 1926 (cited by Karsner).
75. Kirsch, E.: Pathologie des Herzens, Ergebn. d. allg. Path. u. path. Anat. **22**: 1, 1927.
76. Applebaum, E., and Nicolson, C. H. B.: Occlusive Diseases of the Coronary Arteries, AM. HEART J. **10**: 662, 1935.
77. Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8**: 245, 1929.
78. White, P. D.: Heart Disease, New York, 1931, p. 351, The Macmillan Co.
79. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction, Am. J. M. Sc. **183**: 215, 1932.
80. Master, A. M., Dack, S., and Jaffe, H. L.: Coronary Artery Thrombosis—Mode of Death and Analysis of Fatal Cases, N. Y. State J. Med. **37**: 1707, 1937.
81. Meakins, J. C., and Eakin, W. C.: Coronary Thrombosis: A Clinical and Pathological Study, Canad. M. A. J. **26**: 18, 1932.
82. Sprague, H. B., and Orgain, E. S.: Electrocardiographic Study of Cases of Coronary Occlusions Proved at Autopsy at the Massachusetts General Hospital 1914-1934, New Eng. J. Med. **212**: 903, 1935.
83. Hamman, L.: Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**: 273, 1926.
84. Wolff, L., and White, P. D.: Acute Coronary Occlusion, Boston Med. and S. J. **195**: 13, 1926.
85. Barnes, A. R.: Electrocardiogram in Myocardial Infarction, Arch. Int. Med. **55**: 457, 1935.
86. Levy, R. L.: Arteriosclerosis, Including Thrombosis of the Coronary Arteries; In Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Co.
87. Dietrich, A., and Schroeder, K.: Abstammung des Gefässendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. **274**: 425, 1930.
88. Welch, W. H.: Thrombosis, in Papers and Addresses, Johns Hopkins Press **1**: 110, 1920.
89. Clawson, B. J., and Bell, E. T.: The Heart in Syphilitic Aortitis, Arch. Path. **4**: 922, 1927.
90. Packard, M., and Wechsler, J. F.: Aneurysm of the Coronary Arteries, Arch. Int. Med. **43**: 1, 1929.
91. Chiari, H.: Zur Kenntnis der Aneurysmen der Kranzschlagadern des Herzens, Wien. klin. Wchnschr. **51**: 977, 1938.

THE ELECTROCARDIOGRAM DURING ATTACKS OF ANGINA PECTORIS; ITS CHARACTERISTICS AND DIAGNOSTIC SIGNIFICANCE

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INTRODUCTION

IT IS evident from the literature that changes in the electrocardiogram occur during attacks of angina pectoris, but opinions differ concerning the incidence, character, and degree of these changes. Since angina pectoris is commonly regarded as a consequence of relative myocardial anoxia, several investigators have suggested that the earlier stages of coronary arteriosclerosis may be detected by tracings taken following exertion or generalized anoxia. Little attempt has been made, however, to compare the electrocardiographic response of patients with coronary artery disease with that of normal subjects under comparable conditions.

The divergent results and conclusions may be attributed, at least in part, to the different techniques employed. Insufficient attention has been paid to the exact relationship between the time the tracing was taken and the onset or cessation of exercise, anoxemia, or the attack of angina. The attacks of pain are usually short in duration,[1] and are accompanied by rapid changes in the state of the cardiovascular system.[2] Considerable time is required to record the three or four leads of the electrocardiogram, even after both the patient and the instrument are made ready to take the tracing. Missal[3] found that a minimum of one and one-quarter minutes was required, and, with some instruments, as much as six to ten minutes was necessary. Although the electrocardiograms reported in the literature were taken "during" attacks of angina pectoris, it is obvious that the different leads must necessarily have been taken at different times during the attack, and may represent entirely different aspects of the rapidly changing cardiovascular state. It is probable that many tracings were obtained toward the end of the attack of pain, or even after the attack had subsided; this is undoubtedly true in those instances in which the electrodes were applied to the patient and the instrument standardized after the onset of pain.

The purpose of the present investigation was threefold: (1) To observe the relationship of electrocardiographic changes to the onset and cessation of pain by taking tracings *continuously* before, during, and after attacks of angina induced first by exercise, and later by generalized

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anoxemia; (2) to investigate the mechanism producing these changes; and (3) to evaluate the diagnostic significance of the electrocardiographic changes induced by exercise or by generalized anoxemia.

Part I. The Characteristics of the Electrocardiogram Before, During, and After Attacks of Angina Pectoris

Review of the Literature

The electrocardiogram during spontaneous attacks of angina.—Opportunities to obtain such tracings are rare; since 1918, the results in twenty-five cases have been reported.[4, 5, 6, 7, 8, 9, 10, 11, 12, 13] Changes in the S-T segment occurred in nineteen during the attack; these changes consisted of an elevation or depression of the entire segment, or the take-off, in one or more of the three standard leads. Changes in the T wave occurred in nineteen; a decrease in voltage occurred in eighteen patients, eleven of whom developed inversion; one patient showed an increase in the voltage of the T wave in one lead. Changes in the QRS complexes in two cases were reported.

Feil and Siegal[5] found that one of their four patients showed no electrocardiographic change during the attack; other investigators found changes in either the S-T segment or T wave in *all* cases. Shapiro and Smyth,[9] and also Wood and Wolferth,[13] found that the changes during spontaneous attacks and those induced by exertion, in the same individuals, were identical. The precordial lead was used in only one patient,[9] who showed an elevation (old method) of the S-T interval during the attack.

The electrocardiogram following exercise in patients with angina pectoris.—Reports of observations on more than 215 patients are available.[3, 9, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28] The exercise varied in different patients from simple knee bending or raising dumbbells to running up as many as eight flights of stairs; not all developed angina under these conditions. No attention was paid to the temperature of the environment. The 3- or 4-lead electrocardiograms were taken during rest and *after* cessation of exercise. Changes in the S-T segment after exertion were shown by at least ninety-three of the 215 subjects. Four investigators[9, 14, 15, 25] found such changes in each of the fifteen patients they studied; others found such changes in some, but not all, patients. Rihl, Huttmann, and Spiegl,[25] and also Puddu,[24] commented on the change in the angle between the S-T interval and the ascending limb of the T wave. Changes in the T waves were not analyzed by all investigators; such changes apparently occurred in some, but not all, patients. Apparently, forty-two of the 215 subjects showed no changes in the contour of the complexes following exercise. Duchosal and Henny[16, 17] found, by varying the amount of exercise, that the S-T segment and the T wave became altered before angina developed.

Precordial leads were used by seven investigators. Two found that the changes were greatest in this lead;[15, 20] in one investigation[14] a chest

lead only was employed; and four found that the precordial lead was of no special value.[3, 9, 23, 24]

The electrocardiogram during anoxemia induced in patients with angina pectoris.—The effect of induced anoxemia on the electrocardiogram has been studied in fifty-six cases of angina pectoris.[27, 29, 30, 31, 32, 33, 34, 35, 36] Not all of the patients developed angina under the conditions of the studies.

Changes in the S-T segment occurred in twenty-eight subjects; only Dietrich and Schwiegk[29] found such changes in every patient. Variations in the T waves were not analyzed by all investigators; Levy, Barach, and Bruenn[34] found that continued breathing of an atmosphere containing 12 per cent oxygen caused a decrease in the voltage of the T waves in all of the ten patients whom they studied, and that inversion occurred in some instances, whereas Graybiel[30] and Katz[32] and their coworkers found such changes in some, but not in all, cases. Larsen[33] observed no electrocardiographic changes in the three-lead electrocardiograms of four out of the five patients with "myocarditis." Levy, Bruenn, and Russell[35] found that breathing an atmosphere containing 10 per cent oxygen caused S-T and T changes in the precordial lead, as well as in Lead I.

The electrocardiogram in patients with angina pectoris induced by the subcutaneous injection of epinephrine.—Katz, Hamburger, and Lev[37] have shown that adrenalin causes a depression of the S-T segment and a change in the voltage of the T waves in most, but not in all, patients with angina; these changes resembled closely those seen during spontaneous attacks. Levine, Ernstene, and Jacobson[38] found no appreciable or constant change in the contour of the S-T segment, but did note some change in the voltage of the T waves.

METHODS

THE ELECTROCARDIOGRAM DURING, BEFORE, AND AFTER ATTACKS OF ANGINA PECTORIS INDUCED BY EXERTION

Attacks of angina pectoris were induced by having patients repeatedly mount and descend a two-step staircase under standardized conditions in the manner previously prescribed.[39] An electrocardiographic tracing was taken for one full minute with the patient standing at rest, and was *continued without interruption* throughout the exercise, throughout the attack of induced pain, and for one or more minutes after the pain had disappeared. Only one attack and one electrocardiographic lead were studied on any given day.

Twenty patients, sixteen men and four women, were studied. Five of these patients had arterial hypertension (a systolic pressure of 160 mm. Hg, or more, or a diastolic pressure of 90 mm. Hg, or more).

THE INFLUENCE OF BREATHING LOW CONCENTRATIONS OF OXYGEN ON THE ELECTROCARDIOGRAM

Generalized anoxia was induced in sixteen of the twenty patients with angina pectoris according to the method described by Rothschild and Kissin.[36] These patients rebreathed room air for eight to fifteen minutes, and, as a result, lowered

the oxygen concentration of the inspired air to between 8 and 10 per cent. The rebreathing was stopped either when the patient developed pain or when the spirometer was emptied.

Anoxia was also induced in five of the twenty patients with angina by having them breathe an atmosphere of fixed, low-oxygen content for ten minutes, or until precordial pain was experienced. The subjects, while at rest in the recumbent position, breathed from a large spirometer containing room air so diluted with nitrogen that it contained approximately 10 per cent oxygen; the valves were arranged to prevent rebreathing. Analyses of the oxygen content of the mixture were made by the Haldane method. Electrocardiographic tracings were taken *continuously* during these experiments. The precordial lead was studied in each patient, for the greatest changes following exercise occurred in this lead; in some instances one of the standard leads which had shown marked changes following exertion was also studied (usually Lead II); again, only one lead was taken on any day.

TECHNIQUE OF TAKING AND READING THE ELECTROCARDIOGRAPHIC TRACINGS

A string galvanometer electrocardiograph was used in these studies. The skin resistance changed frequently during the course of the experiment, making it necessary to restandardize frequently. The arm electrodes were attached just below the insertion of the deltoid muscle to minimize somatic tremor and the effects of skeletal muscle contraction; this precaution was of value only in Leads I and IV. A limb electrode (1.5 by 2.5 inches) was used for the precordial electrode because the circular, 3 cm. electrode was found to move during exercise.

These studies were carried out before the present methods for taking precordial leads were adopted; for convenience, the precordial lead was taken on Lead II, with the right arm electrode in the fifth intercostal space at the midclavicular line, and the left leg electrode on the left arm. The curves were interpreted in accordance with the present accepted methods, i.e., an upright wave was called a negative deflection, and an elevation of the S-T segment was termed a depression. In measuring the electrocardiogram, the P-R interval was taken as the isoelectric level; measure-

TABLE I

FREQUENCY OF CHANGES IN THE ELECTOCARDIOGRAPHIC COMPLEXES OF TWENTY PATIENTS DURING ATTACKS OF ANGINA PECTORIS INDUCED BY EXERTION

	NUMBER OF PATIENTS SHOWING CHANGES IN ONE OR MORE LEADS	NUMBER OF TRACINGS SHOWING CHANGES					CHARACTER OF CHANGES			
		TOTAL	LEAD I	LEAD II	LEAD III	LEAD IV	VOLTAGE INCREASED *	VOLTAGE DECREASED	DIPHASIC OR INVERTED	NOTCHED SLURRED OR SPREAD
P	8	11	2	2	2	5	9	2	0	0
P-R	14	23	5	7	4	7	8	15		
QRS	17	38	12	7	6	13	4	34	0	1
S-T	20	59	10	9	11	20	7	43	9†	
T	19	33	7	5	7	14	18	15	9†	1
Total number of patients or leads	20	76	20	18	18	20				

*Increased voltage of P, QRS, and T waves. Nine leads in five patients.
Elevation of S-T segment.
Prolongation of P-R interval.

†In two patients, an upright T wave became diphasic (Leads I and IV); in two, a negative T wave became positive (Lead IV); in one, a T wave diphasic with the patient at rest became completely inverted or more strikingly diphasic (Leads I, II, and IV).

ments using the T-P interval as the isoelectric level gave similar results, but in many instances the increase in both heart rate and P-wave size following exertion caused obliteration of the T-P interval. Variations of less than 0.1 mv. in the voltage of the P or T waves or in the level of the S-T segment, changes of less than 0.3 mv. in the QRS voltage (measured as the sum of the positive and negative excursions), and changes of less than 0.04 second in the duration of the P-R interval were difficult to measure accurately, and hence were ignored.

RESULTS

THE ELECTROCARDIOGRAM DURING, BEFORE, AND AFTER ATTACKS OF ANGINA PECTORIS INDUCED BY EXERTION

The character of the electrocardiographic changes during attacks of angina is best illustrated by tracings recorded *immediately* after the cessation of exercise; this was within a few seconds after the beginning of

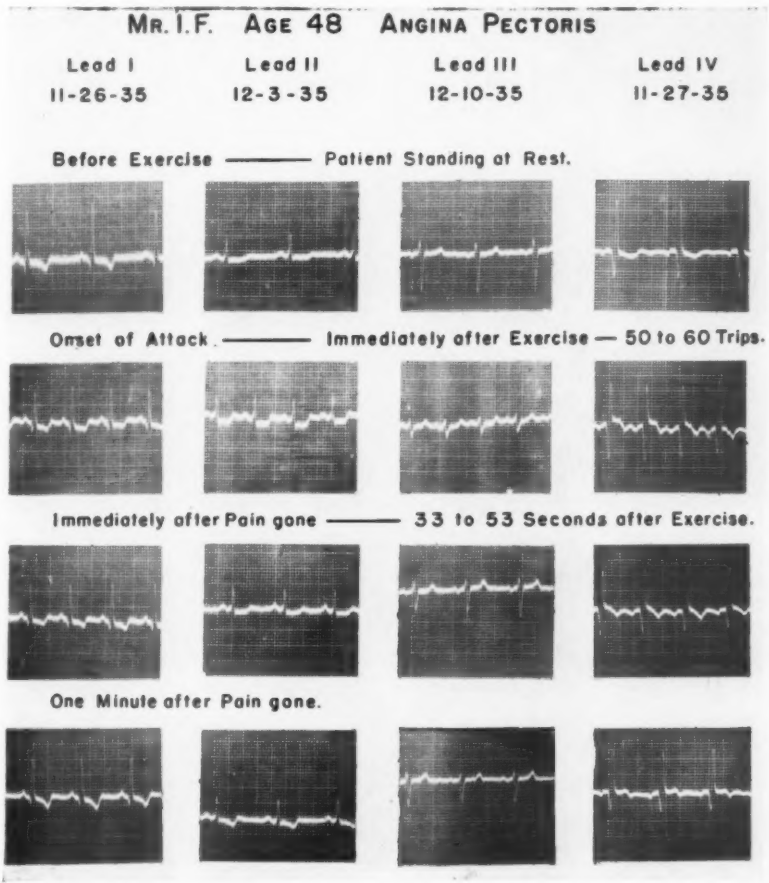

Fig. 1.—Changes in the electrocardiogram during and after attacks of angina pectoris induced by exercise (selected portions of continuous tracings taken during and after exertion on four different days). The electrocardiogram at the onset of pain, when compared with tracings taken at rest, shows a decrease in the voltage of QRS in Leads I and III; a depression of the S-T segment in Leads I, II, and IV (Lead IV taken by the old method); and slight changes in the T waves of all leads. Immediately after the pain had disappeared, the changes in the S-T segments became less pronounced. One minute after the cessation of pain the S-T segments became practically isoelectric; the T wave in Lead IV has become diphasic, the QRS complexes have not yet returned to their original voltage.

cardiac pain (Table I, Figs. 1, 2, and 3). A total of seventy-six leads was obtained; all four leads were taken in eighteen patients, and only Leads I and IV in the remaining two.

Changes in voltage were by far the most frequent; variations of form, although striking, were comparatively uncommon, and were usually accompanied by a change in voltage. The four-lead electrocardiogram, taken under the usual clinical conditions, with the patient at rest, showed abnormalities indicative of coronary artery disease in ten of the twenty patients. There was no conspicuous difference between the response of those with normal and those with abnormal electrocardiograms at rest, or between those with hypertension and those with normal arterial pressure.

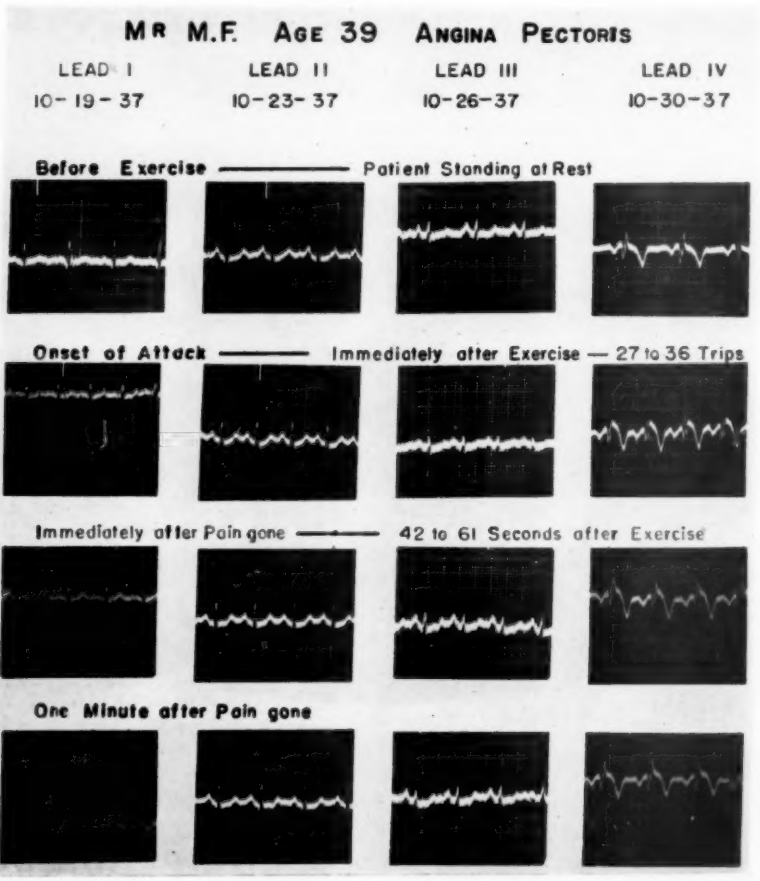

Fig. 2.—Changes in the electrocardiogram during and after attacks of angina pectoris induced by exercise (selected portions of continuous tracings taken during and after exertion on four different days). At the onset of pain the S-T segment in Lead IV (taken by the old method) became markedly depressed, as compared with the tracings taken while at rest, while Leads II and III show very slight depression (less than 1 mm.), and the voltage of T_4 has increased. By the time the pain disappeared the T waves became more prominent in Leads I and III; one minute later the S-T segment in Lead IV still showed some depression, as compared to the tracings taken while at rest.

Deviation of the S-T segment was the most common change. This occurred *most often in Lead IV, where it was found in all of the twenty patients;* in three patients S-T changes were found in the precordial lead only. The magnitude of the changes varied from 0.1 to 0.15 mv. in thirty-one instances, and from 0.15 to 0.3 mv. in nineteen tracings; in all of the latter there was a depression. The change usually occurred in the first third of the S-T segment. A positive Pardee's sign was found once.

Changes in the T wave were striking, but were not as common at the onset of pain as were the S-T changes. The magnitude of the changes varied from 0.1 to 0.15 mv. in twenty-two instances, and from 0.15 to 0.55 mv. in the remaining eleven. Changes in the P waves were not striking. Changes in the P-R interval were of little significance except in one instance, in which the duration increased from 0.18 to 0.22 second. Changes of 0.3 to 0.5 mv. in the voltage of the QRS complexes occurred in nineteen tracings; nineteen others showed changes greater than 0.5 mv.; two patients showed changes greater than 1 mv. (1.5 and 2.7 mv., respectively). In four instances changes in voltage occurred rhythmically, apparently with respiration. Three patients showed an increase of 3 to 4 mm. in the amplitude of S_2; no patient developed a more prominent Q_3. Two patients, whose initial deflection of QRS_4 was

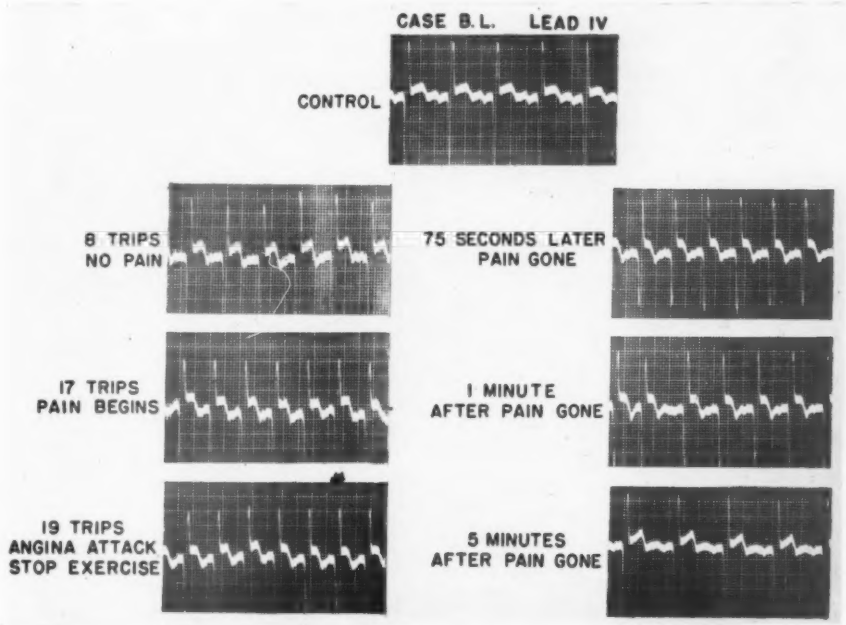

Fig. 3.—Changes in the precordial lead (old method) before, during, and after an attack of angina pectoris induced by exertion. Changes in the S-T segment and T wave began shortly after the onset of exercise, and increased only slightly until the patient was forced to stop because of pain. Further changes, especially in the T waves, occurred after the pain had disappeared.

negative during rest, developed a positive initial deflection during exercise. In no instance did a positive initial deflection disappear during exertion.

The time of onset of the electrocardiographic changes during exercise could be ascertained readily in Leads I and IV because the complexes in these leads were not obliterated by the tremor of exertion. Changes in the electrocardiogram usually became evident after ten to fifteen trips, whereas pain did not begin until twenty to seventy trips had been made. The early changes were quite similar to those observed after pain had developed, but were usually slightly less pronounced (Fig. 3).

Changes in the electrocardiogram after the disappearance of pain.—Cardiac pain continued for 15 to 150 seconds after the cessation of exercise in these twenty patients. The changes in the electrocardiogram which had become evident at the onset of pain either diminished or disappeared in about one-half of the tracings, whereas they either persisted or became more pronounced in the other half (Table II). Of the

TABLE II

CHANGES IN THE ELECTROCARDIOGRAPHIC COMPLEXES AFTER THE CESSATION OF AN ATTACK OF ANGINA PECTORIS INDUCED BY EXERTION, COMPARED WITH THOSE OBSERVED DURING THE HEIGHT OF PAIN (76 LEADS IN 20 PATIENTS)

	AT ONSET OF PAIN	IMMEDIATELY AFTER DISAPPEARANCE OF PAIN				
	NUMBER OF LEADS SHOWING ELECTROCARDIOGRAPHIC CHANGES	FURTHER CHANGES IN ELECTROCARDIOGRAM				NEW OR ADDITIONAL CHANGES
		CHANGES DIMINISHED	CHANGES DISAPPEARED	CHANGES INCREASED	NO FURTHER CHANGES	
P	11	2	5	1	3	3
P-R	23	1	11	1	10	1
QRS	38	12	5	1	20	3
S-T	50	18	7	8	17	6
T	33	8	6	3	16	9
		ONE MINUTE AFTER DISAPPEARANCE OF PAIN				
P		1	5	2	3	7
P-R		1	14	3	5	1
QRS		10	14	6	8	6
S-T		20	14	7	9	9
T		4	12	11	6	22

patients who showed no S-T or T changes at the onset of pain, about one-fourth developed such variations before the pain disappeared (Table II, Figs. 1, 2, and 3).

After the pain had subsided, further changes developed in many instances. An increase in the amplitude of the T wave occurred in about one-third of the tracings. Diphasic T waves became evident in ten of the twenty cases (usually in Leads IV and I); in three of these instances diphasic T waves had been present during rest or at the onset of pain.

The total duration of the abnormalities induced by exertion was not ascertained; one minute after the pain had subsided, 20 per cent of the tracings still showed changes as compared with the resting electrocardiogram; in one case the changes persisted for several hours, whereas in another they persisted for more than five minutes after the disappearance of pain. The duration of the alterations in the electrocardiogram bore no constant relationship to the changes in heart rate during or following exercise.

THE EFFECT OF BREATHING AN ATMOSPHERE CONTAINING A LOW CONCENTRATION OF OXYGEN

With the rebreathing method of Rothschild and Kissin,[41] we were able to induce slight precordial distress in only one of sixteen patients, although attacks could be induced regularly in all of these patients by the standardized exercise tolerance test. Only one patient (who, incidentally, did not develop pain) showed electrocardiographic changes during the period of rebreathing.

When anoxemia was induced by having patients breathe an atmosphere of constantly low oxygen content, four of the five patients developed precordial pain similar to that experienced in daily life or during the standardized exercise tolerance test. All five patients developed changes in the electrocardiogram which were similar in all respects, except for heart rate, to those observed in the *same* patients during attacks induced by exercise (Fig. 4). Here, again, the electrocardiographic changes began before the onset of pain and persisted after the disappearance of anoxemia and pain (Table III).

TABLE III

EFFECT OF BREATHING ATMOSPHERES CONTAINING LOW CONCENTRATIONS OF OXYGEN ON THE ELECTROCARDIOGRAM OF PATIENTS WITH ANGINA PECTORIS

CASE	DURATION OF ANOXEMIA	PER CENT OXYGEN	TIME OF ONSET OF EKG CHANGES	DURATION OF EKG CHANGES*	ATTACK OF ANGINA
	Minutes		Minutes	Minutes	
B. L.	3.1	9.39	1	2	yes
H. B.	6.6	10.08	3	2	yes
B. A.	10.0	11.71	8	1−	no
	6.3	9.92	4	3	yes
L. W.	6.0	10.08	4	2	no
	5.2	8.89	4	5+	yes
H. S.	10.0	10.05	7	5+	no

*After cessation of breathing low oxygen concentration.
−Less than 1 minute.
+More than 5 minutes.

COMMENT

It is evident from the literature that changes in the level of the S-T segment and in the voltage of the T waves may be found in the tracings of some, but not of all, patients during attacks of angina. It is also evident that the changes which occur are similar, regardless of whether the

attacks occur spontaneously or are induced by exercise, generalized anoxemia, or adrenalin. Opinions differ not only concerning the frequency, character, and degree of these changes, but also concerning the relative importance and frequency of alteration of the level of the S-T segment and of changes in the direction or voltage of the T wave. The few investigators who have obtained precordial leads do not agree on the results.

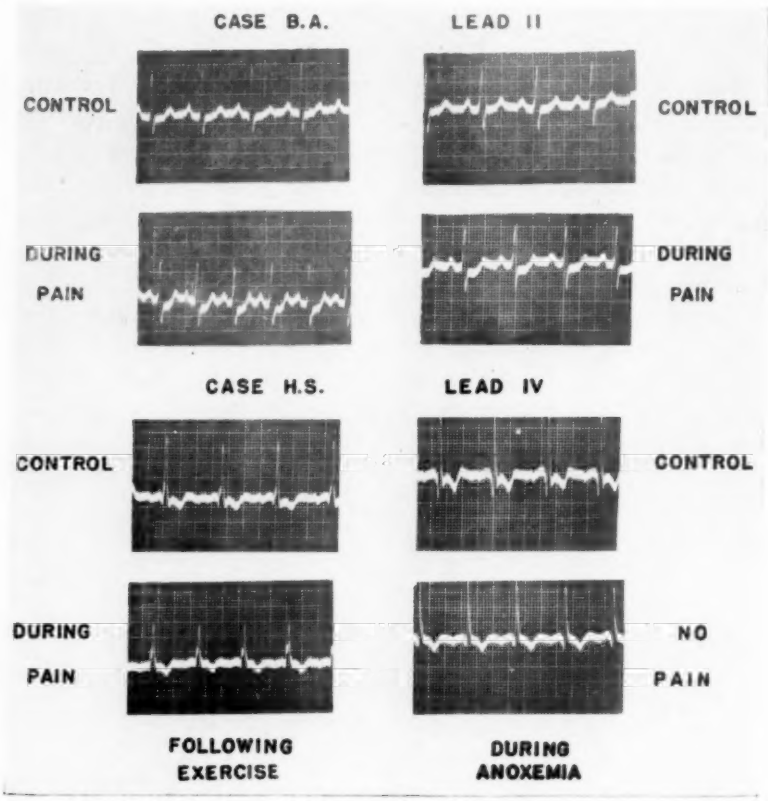

Fig. 4.—The similarity of the electrocardiographic changes during attacks of pain induced by exercise and those observed during generalized anoxemia.

When electrocardiographic tracings are taken *continuously*, as in the present investigation, it becomes evident that changes in the character of the curves begin soon after the onset of exercise or anoxemia, increase slightly until the patient is forced to stop because of pain, and then subside rapidly or assume a somewhat different character. They may occur in all leads, but are most common and most striking in the precordial lead. The most common change during the height of the pain is a depression or an elevation of the S-T segment, accompanied by a change in the contour of this part of the curve. Changes in the voltage of the T waves are common, but do not always occur; such changes are more

frequent after the attack has persisted for some time or after the pain has disappeared. Variations in the P waves, QRS complexes, and P-R intervals are slight.

The similarity of electrocardiograms following exertion or an attack of angina to those following coronary occlusion may be of considerable practical importance. Exercise or emotion insufficient to induce an attack of angina may nevertheless cause changes in the electrocardiogram. A single tracing taken to establish the diagnosis of myocardial infarction is of little value, and, in fact, may give false information unless the patient has been at rest and has experienced no angina for some time (at least fifteen minutes, and longer in some instances) before the tracing is recorded.

The attempt to precipitate attacks by inducing generalized anoxemia is of little practical value in the diagnosis of angina pectoris. The rebreathing method of Rothschild and Kissin induces attacks in only a small percentage of patients with angina. Continuous breathing of an atmosphere containing 10 per cent oxygen is more likely to induce pain, but here, again, patients with obvious angina may fail to develop an attack.

The electrocardiogram during an attack of spontaneous chest pain is not only difficult to obtain, but also appears to be of little value in establishing the diagnosis of angina pectoris or coronary artery disease. Although depression or elevation of the S-T segment in the precordial lead is observed frequently during an attack of angina, the fact that such a change may occur before the onset of pain indicates its lack of specificity. Furthermore, as will be shown, similar changes can be induced in normal persons who have no heart disease.

Part II. The Mechanism Underlying the Electrocardiographic Changes During Attacks of Angina Pectoris

It is now generally agreed that attacks of angina pectoris are caused by relative myocardial anoxemia and its sequelae.[40] It has been demonstrated that attacks of angina can be induced by anoxemia,[41, 42] and also that the amount of work which can be accomplished by some patients before they experience pain can be increased if they breathe a high concentration of oxygen before and during exercise.[43]

The present studies show that the electrocardiographic changes during attacks of angina induced by generalized anoxemia are comparable to those observed in the *same* patients during angina induced by exercise (Fig. 4). It is likely, therefore, that the electrocardiographic changes also are secondary to myocardial anoxemia. The following experiments afford additional evidence in favor of this view, for they show that breathing high concentrations of oxygen before and during exercise may delay the electrocardiographic changes which would otherwise occur.

METHODS

The minimum amount of work required to induce changes in the S-T segment of Lead IV was ascertained in four patients with angina pectoris by having each perform decreasing amounts of work on successive days. On a subsequent day the patient inhaled undiluted oxygen for ten minutes while standing at rest; then, while continuing to breathe oxygen, he repeated the minimum amount of work which previously caused S-T changes.

A series of Douglas bags connected to a stationary manifold served as a reservoir for the oxygen. Rubber tubing with an inside diameter of ¾ inch was led from this reservoir to the patient in a manner which did not interfere with the exercise.

An electrocardiogram was taken before the test was begun, after breathing oxygen for nine and three-quarters minutes while the patient was still standing at rest, continuously during the exercise, and for two minutes thereafter. The technique of taking the electrocardiograms and the methods of measuring the tracings in these experiments were similar to those described in Part I. Results were accepted only if they could be duplicated on a subsequent date.

RESULTS

The minimum amount of exertion necessary to induce electrocardiographic changes in the four patients studied proved to be 17, 25, 40, and 60 per cent, respectively, of the amount of work necessary to induce pain. When these patients performed the same amount of exercise while breathing pure oxygen, three of the four showed no electrocardiographic changes (Fig. 5). Breathing oxygen under the same conditions failed to prevent the electrocardiographic changes induced by five to ten trips more than the minimum necessary to cause changes when breathing room air.

Part III. Electrocardiographic Changes After Exercise as Diagnostic Criteria of Angina Pectoris or Coronary Disease

Electrocardiographic changes following exertion can be used as objective evidence of angina pectoris only if the response of normal subjects differs materially from that of patients with angina. A survey of the literature, however, does not reveal sufficient information concerning the electrocardiographic response of normal individuals and also of patients with angina after *identical* exertion. The purpose of the present investigation is to compare the tracings of normal subjects and patients with angina after performing the same task, in order to evaluate the practical significance of this procedure in diagnosis.

REVIEW OF THE LITERATURE

Scherf and Goldhammer, in 1933,[19, 27] after studying the 3-lead electrocardiograms of patients with angina pectoris following knee bending or running rapidly up 64, 96, or 128 steps, concluded that a depression of the S-T segment, greatest in Lead II, was diagnostic of coronary artery disease. Control studies on normal subjects were not described; moreover, eight of forty patients with definite angina showed no such changes. Von Mentzigen[22] stated that negativity of the S-T segment

after bending the knees ten times indicated severe myocarditis. This conclusion was based on a study of 2300 normal and ill persons, but no statistics were presented, and three of his illustrations showed depression of the S-T segment in normal subjects. Duchosal and Henny,[16, 17] using varying amounts of exercise for different patients, concluded that a depression of the S-T segment, plus a depression or inversion of the T wave, indicated myocardial ischemia. Cardiac patients without angina pectoris and normal subjects failed to show such changes after exhausting work; however, in sixteen of thirty-one cases of known angina there were no changes, and in two of seventy-two normal subjects there were definite or doubtful changes. Missal[3] found T and R-T changes in the electrocardiogram during angina induced by exercise, and concluded that this may be of diagnostic value in doubtful cases; studies on normal controls were not reported. Faliero,[18] without presenting complete data, concludes that in 32 per cent of cases of angina pectoris electrocardiographic changes are produced by work. Raab and Schönbrunner[44] have

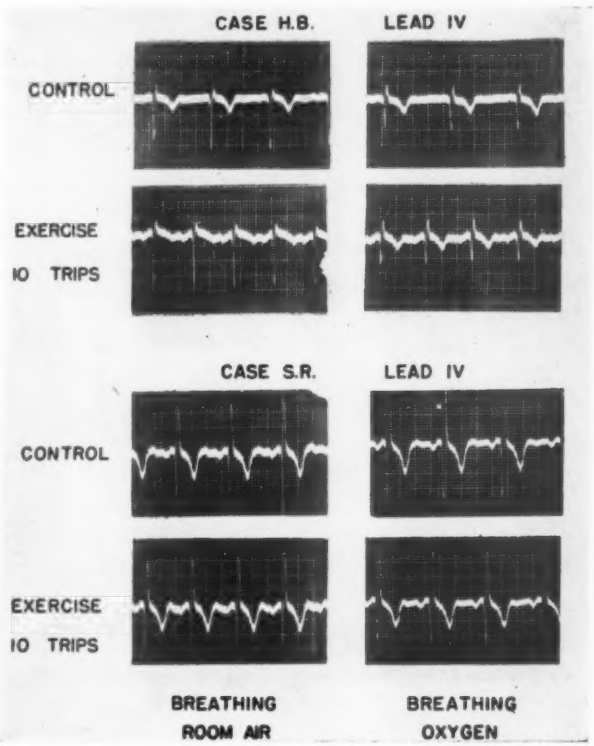

Fig. 5.—The effect of breathing oxygen before and during exercise, showing minimal electrocardiographic changes induced by small amounts of exercise while breathing room air, and prevention of these changes on performing the same amount of work while breathing pure oxygen (precordial leads taken by old method).

The electrocardiograms of patient S. R. show a slight depression (about 0.5 mm.) of S-T (as compared with P-R) while at rest, and a slight elevation of S-T after exercise while breathing room air, but not while breathing oxygen.

Patient H. B. shows definite negativity of the S-T segment and definitely decreased voltage of the T waves after exercise while breathing room air; these changes do not occur on performing the same amount of work while breathing oxygen.

used the electrocardiogram after exercise to demonstrate improvement after treatment by X radiation of the adrenals. Puddu,[24] alone of this group, has studied the electrocardiographic response of subjects without, as well as with, angina pectoris to an identical task. Nine of his fourteen patients with angina showed greater changes in the electrocardiogram following exertion than were observed in any of the ten normal subjects studied; the response of the remaining five patients with angina was similar to that observed in the normal subjects. Missal[3] and Puddu[24] found that the precordial lead sometimes yielded positive information when the conventional three leads showed nothing.

Other investigations suggest that the electrocardiogram after work has little diagnostic significance. Wood and Wolferth,[13] who studied the electrocardiogram during induced attacks of angina pectoris, found, in 1931, that fifteen of thirty patients showed no more electrocardiographic changes during attacks than did normal subjects after exhausting exercise. Rosenberger,[45] in 1934, found that sixteen of eighteen young normals showed changes in the S-T segment after work which were similar to those reported by others to be of diagnostic value.

The electrocardiogram of normal subjects following exertion.—Einthoven,[46] in 1908, and Messerle[47] made no comment about the S-T segment after strenuous exertion, but each published two illustrations showing that changes occurred in normal subjects. Hoogerwerf[48] found that 10 per cent of Olympic athletes, after exertion, showed changes, especially in the level of the S-T segment, of a magnitude similar to that which occurs in myocardial infarction. Jezierski[49] found a depression of the S-T segment in many soldiers after strenuous marching; Cooper, O'Sullivan, and Hughes[50] found similar changes after a rowing race. Zettel and Fink[51] found comparable changes in young normals who exercised while wearing gas masks. Bramwell and Ellis[52] made no comment about the S-T segment after exercise, but called attention to a decrease in the voltage of the T wave in some normal subjects, and an increase in others. These investigators studied only the conventional three leads. Bierring, Larsen, and Nielsen,[14] who studied the precordial lead only, found that work on a bicycle ergometer caused a depression of the S-T segment.

METHODS AND MATERIALS

The series studied consisted of fifteen patients with angina pectoris and fifteen normal subjects. Ten of the fifteen patients with angina were selected because they belonged to the original group of twenty reported in Part I; the remaining five patients with angina were similar clinically. Ten of the fifteen normal subjects were medical students, interns, or laboratory workers; they were between 25 and 31 years of age, and were chosen because of their youth, health, activity, and freedom from any suggestion of heart disease. The remaining five normal subjects were members of the hospital maintenance department, 48 to 73 years of age, and were employed at moderately hard physical labor. These latter subjects had slight, or no, arteriosclerosis, as judged by ophthalmoscopic and physical

examination, and no evidence of heart disease, insofar as one could tell by the history, physical examination, blood pressure measurements, and standard four-lead electrocardiograms.

The exercise consisted of mounting and descending the two-step staircase twenty times (twenty trips), as in previous studies.[39] This requires little or no training, and causes little emotional reaction. The temperature of the room was maintained constantly at 45° F. to 50° F. because patients with angina are more likely to develop pain, and their exercise tolerance is more constant, in this relatively cold environment than at ordinary room temperature. All tests were carried out at least one hour after a light breakfast, and all medication was avoided for at least twelve hours prior to the test. The patient rested for at least fifteen minutes before the test was begun; one hour was allowed to elapse if pain had been experienced recently; as a rule, only one test was performed on each subject, but the results were checked by repetition in some subjects, and in the patients with angina by comparison with tracings taken during an induced attack.

A control tracing, fifteen seconds in duration, was taken with the patient standing at rest. The standard exercise was then performed, with the electrodes still in place, and the machine, but not the camera, running continuously. The camera was started immediately before the cessation of work, and continued to run for fifteen seconds after the exercise was stopped. In many instances, additional fifteen-second strips were photographed one, two, and three minutes after stopping the exercise.

The precordial lead only was employed in this investigation, for previous studies had indicated that the greatest changes might be expected in this lead. The tracing was taken with the lead switch on II, with the left leg electrode in the fifth intercostal space at the midclavicular line, and with the right arm electrode on the right arm immediately below the insertion of the deltoid. According to the present nomenclature, this is Lead IVR, and an upright wave indicates relative positivity of the precordial electrode. Some subjects showed more striking changes in the precordial lead when the right, instead of the left, arm was used; in others the reverse was true, but in most instances it made little difference which arm was used.

A vacuum-tube electrocardiograph* was employed, and proved more satisfactory than the string galvanometer for the purpose of this study, for it was simpler and quicker to operate, did not require frequent restandardization, and showed less wandering of the baseline. Tracings taken with the two types of instruments, and on the same subjects, both before and after exercise, were identical for all practical purposes.

RESULTS

The patients with angina pectoris, after twenty trips over the two-step staircase, showed changes in the electrocardiogram which were comparable to those observed during the height of the pain. Only two patients developed angina under the conditions of the study; in the remaining thirteen patients the exercise was 32 to 83 per cent of the amount necessary to induce pain.

Changes in the P waves and QRS complexes were few; changes in the S-T segments and T waves were frequent and striking (Table IV, Fig. 6). The level of the S-T segment became depressed more than 2 mm. in two patients, from 1 to 2 mm. in eleven, and did not change essentially in the remaining two patients. Changes in the T waves of more than

*Sanborn Cardiette.

2 mm. were observed in nine patients, four of whom showed a decrease of 2 to 7 mm., and five an increase of 2 to 4 mm. The type and degree of change in the S-T segment or T wave did not depend upon the character of the four-lead electrocardiogram taken under the usual clinical conditions, except that one patient who had a diphasic T wave in Lead IV while at rest showed an exaggeration of this characteristic after exertion.

The normal subjects showed changes in the electrocardiogram after twenty trips which were similar to those observed in the patients with angina pectoris in some respects, and different in others.

An increase in the voltage of the P wave occurred in five subjects. Changes in the level of the S-T segment not exceeding 1 mm. occurred in ten subjects; the remaining five developed changes in the S-T level of 0.5 mm., or less. A decrease of 2 mm. to 7 mm. in the amplitude of the T wave occurred in thirteen subjects; no patient developed an increase in the voltage of the T wave. Six subjects showed a definite notching, amounting almost to a reduplication, of the T wave, following exercise. A similar degree of notching was not observed in patients with angina, except occasionally when exercise was performed following medication. The changes in the ten young normals were not materially different from those observed in the five older subjects without heart disease, except that four of the young normals developed a decrease of more than 5 mm. in T-wave amplitude, whereas only one of the older subjects showed a similarly large decrease.

TABLE IV

FREQUENCY OF ELECTROCARDIOGRAPHIC CHANGES (PRECORDIAL LEAD) IN 15 PATIENTS WITH ANGINA PECTORIS, AND 15 SUBJECTS WITHOUT HEART DISEASE, AFTER AN IDENTICAL TASK

	PATIENTS WITH ANGINA PECTORIS	NORMALS WITH NO HEART DISEASE
P Wave		
Change of less than 1 mm.	12	10
Decrease in amplitude 1 mm.	1	0
Increase in amplitude 1 mm.	2	5
QRS Complex		
Change of less than 3 mm.	11	7
Decrease in amplitude 3 mm. to 5 mm.	3	6
Increase in amplitude 3 mm. to 4 mm.	1	2
S-T Segment		
Change of less than 1 mm.	2	5
Depressed 1 mm.	8	10
Depressed 1.5 mm. to 2.5 mm.	5	0
T Wave		
Change of less than 1 mm.	1	0
Decrease in amplitude 1 mm.	4	2
2 mm. to 4 mm.	2	8
5 mm. to 7 mm.	2	5
Increase in amplitude 1 mm.	1	0
2 mm. to 4 mm.	5	0

COMMENT

The amount of exercise used in these studies (roughly comparable to climbing two flights of stairs[39]) was selected only after considerable experiment. Larger amounts of work were not practical, for the majority of patients with angina developed pain after twenty-five to thirty-five trips; smaller amounts proved to be inadvisable because many patients with angina failed to show electrocardiographic changes after less than twenty trips.

In general, patients with angina pectoris are more likely to develop a depression of the S-T segment of more than 1.5 mm., or an increase in the voltage of the T wave. On the other hand, patients with angina are less likely to show an increase in the voltage of the P wave, or a marked decrease in the voltage, or a deep notching, of the T wave. This marked decrease in T-wave voltage in young normals after exertion is similar to

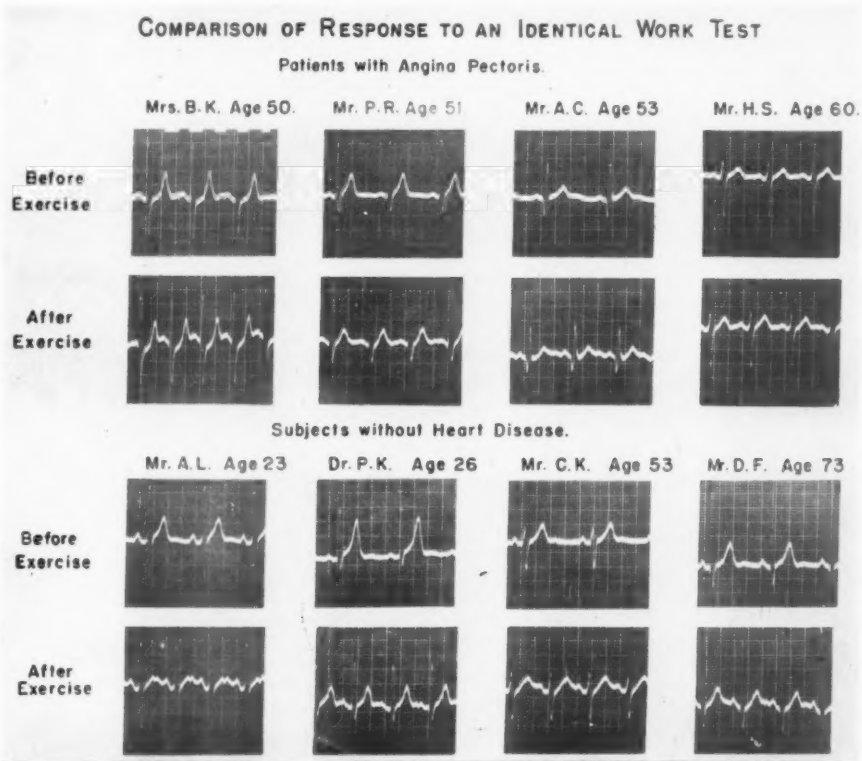

Fig. 6.—Patient B. K. shows changes in the S-T segment which are greater than those observed in the normal subjects and in most of the patients with angina.

Patients P. R. and A. C. show the more common degree of depression of the S-T segment in patients with angina; this is similar to the degree of change observed in normal subjects A. L., P. K., and C. K.

Patient H. S. and normal subject D. F. show little or no change in the level of the S-T segment.

Normal subjects A. L. and P. K. show a more marked decrease in the voltage of the T wave than is usually seen in patients with angina pectoris. (Precordial lead taken by new method; Lead IVR).

the T-wave changes in young subjects observed by May[53] during generalized anoxemia. These changes in the S-T segments and T waves are probably the expression of the local oxygen debt which follows muscular activity.

The response of the electrocardiogram to exercise does not appear to be of great practical value in the diagnosis of coronary artery disease. Of thirty subjects (fifteen normal and fifteen with angina), more than half showed definite changes in the S-T segment which were so similar that it was impossible to distinguish between the tracings of a young healthy subject and those obtained from patients during an attack of angina pectoris. If the changes are considered significant, the test yields a false positive result in two-thirds of normal persons. On the other hand, two patients with angina showed no definite change in the electrocardiogram after exercise, indicating that the test may yield a false negative result in certain patients with definite coronary artery disease.

One-third of the patients with angina showed changes in the S-T segment which were greater than those observed in any of the normal subjects in this series. This may be of importance, but in two of these five patients the change in the S-T segment was only slightly greater than that observed in our normal subjects, and no greater than that in some of the normals studied by Rihl, Huttmann, and Spiegl,[25] Hoogerwerf,[48] and Rosenberger;[45] a larger series of normal subjects (especially those in the coronary artery disease age group) will have to be studied before one can be certain that, occasionally, normal persons may not show even greater changes. The practical value of these changes is further decreased by the fact that three of the five patients who showed comparatively great changes after exertion had abnormalities of the standard four-lead electrocardiogram at rest, so that the result of the test gave little additional information. It is evident, therefore, that the effect of exercise on the electrocardiogram of normal subjects and on that of patients with angina pectoris is not sufficiently different to be of diagnostic value.

Part IV. Electrocardiographic Changes During Generalized Anoxemia as a Diagnostic Criterion of Angina Pectoris or Coronary Artery Disease

Introduction and review of the literature

The purpose of this investigation is to compare the electrocardiographic response of normal subjects with that of patients with angina pectoris, in order to evaluate the diagnostic value of this procedure.

Katz, Hamburger, and Schutz[32] studied the conventional three-lead electrocardiogram obtained during anoxemia induced by rebreathing room air. They found that anoxemia caused a depression of the S-T segment and a diminution in the amplitude of the T wave which occasionally led to inversion in normal subjects and also in patients with

angina pectoris. These results have been confirmed by Larsen,[33] Dietrich and Schwiegk,[29] Rothschild and Kissin,[36] Graybiel, Missiuro, Dill, and Edwards,[30] and Levy, Barach, and Bruenn,[34] but are contrary to those of Levy, Bruenn and Russell.[35*]

METHODS

The method of taking electrocardiograms during induced anoxia has already been described in Part I. For the purpose of this analysis the tracings of the five patients who developed changes while continuously breathing an atmosphere containing approximately 10 per cent oxygen (Part I) were compared with the tracings of eight normal subjects who were studied under similar conditions. Four of the five patients with angina developed pain during anoxemia experiments. Five of the normal subjects were 25 to 30 years of age; the remaining three were between 50 and 55. Only the precordial lead was used, for previous studies (Part I) indicated that the greatest changes might be expected in this lead; in the patients with angina these were taken according to the old method, using the apex and the left arm; in the normal subjects the tracings were taken according to the newer technique, using the apex and the right arm (Lead IV R).

RESULTS

The results in the patients with angina have been described in Part I. Briefly, electrocardiographic changes occurred in each of the five patients who breathed an atmosphere containing approximately 10 per cent oxygen (Table V, Fig. 7). All five patients developed a change of at

TABLE V

FREQUENCY OF ELECTROCARDIOGRAPHIC CHANGES (PRECORDIAL LEAD) INDUCED BY ANOXEMIA IN 5 PATIENTS WITH ANGINA PECTORIS AND 8 SUBJECTS WITHOUT HEART DISEASE

	5 PATIENTS WITH ANGINA PECTORIS	8 NORMALS WITH NO HEART DISEASE
Changes in the level of the S-T segment		
Change of less than 1 mm.	0	5
Depressed 1 mm.	1	1
Depressed 2 to 2.5 mm.	2	0
Elevated 1 mm.	2	2
Changes in the amplitude of the T wave		
Change of less than 1 mm.	1	1
Decreased 1 mm.	1	1
2 to 3 mm.	1	4
5 mm.	0	2
Increased 3 to 5 mm.	2	0
Inverted or diphasic	1[1]	0

[1]This person showed a diphasic T wave before the induction of anoxemia, as well as after.

*Levy, Bruenn, and their co-workers have published three studies of electrocardiographic changes in man following induced anoxemia. In the first investigation,[34] an atmosphere containing 12 per cent oxygen was used, and similar changes were induced in the electrocardiograms of normal subjects and patients with angina. In the second study,[35] a mixture containing 10 per cent oxygen was breathed, for as long as twenty minutes, if necessary, to differentiate between the electrocardiographic response of normals and that of patients with coronary heart disease. Although most investigators agree that few patients with angina show inverted or diphasic T waves during attacks, Levy, Bruenn, and Russell[35] have utilized such changes to differentiate between normals and abnormals. Six of their patients with old coronary occlusion showed a "normal response" of the electrocardiogram to anoxemia; two of these six developed substernal discomfort during the test. The third report appeared after the present investigation was submitted for publication. In this third study (Levy, Bruenn, and Williams, Effects of Induced Anoxemia in Patients with Coronary Sclerosis as Modified by Certain Drugs, Trans. Assoc. Am. Phys. 54: 244, 1939), it was found inadvisable to attach any significance to T-wave changes.

least 1 mm. in the level of the S-T segment. Two patients developed a depression of 2 and 2½ mm., respectively; one of these two showed evidence of coronary artery disease in the standard four-lead electrocardiogram which was taken at rest (diphasic T waves in Leads I, II, and IV). Changes in the voltage of the T wave occurred in two of the five patients. No patient developed a diphasic or inverted T wave as the result of anoxia, but the one patient who had a diphasic T_4 during rest showed an accentuation of this phenomenon as a result of the S-T depression.

Three of the eight normal subjects developed a change of 1 mm. in the S-T level; none showed a greater change. Seven showed a decrease of 0.2 to 0.5 mv. in the voltage of the T wave; no subject developed an inverted or diphasic T in Lead IV R.

COMMENT

In general, anoxemia, like exercise, is more likely to induce a depression in the S-T segment of more than 1.5 mm., or an increase in the

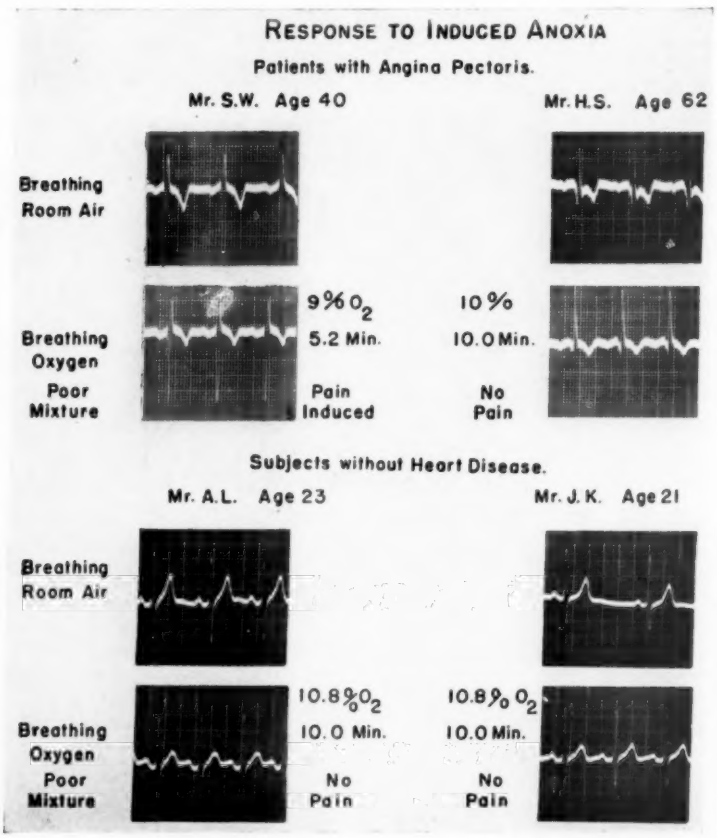

Fig. 7.—Patient S. W. shows a slight change in the level of the S-T segment and the voltage of the T wave during an attack of pain induced by breathing an oxygen-poor mixture (precordial lead taken by the old method). These changes are comparable to those observed in normal subjects A. L. and J. K. (precordial leads taken by the new method), and less than those observed in a patient (H. S.) with angina pectoris who, however, failed to develop pain under these conditions.

T-wave voltage, in patients with angina than in normal subjects. The difference between the response of the two groups was more striking after anoxia than after exertion, and it would seem that the stimulus of generalized anoxemia approached the requirements for a diagnostic test more closely than did the stimulus of exertion. There are, however, two factors which weigh heavily against general acceptance of an anoxemia test as a clinical diagnostic measure; the first is concerned with its accuracy, the second with its technical difficulties and potential dangers.

Although it appears to be true that some patients with angina pectoris are likely to develop greater S-T changes than do normal subjects, the changes as a whole are qualitatively similar, and it is frequently difficult to tell from the electrocardiogram alone whether or not the individual has coronary artery disease.

The technical difficulties and possible dangers are definite drawbacks to general use of an anoxemia test. The occasional untoward effects of anoxia are well known. Schneider and Truesdale,[54] and also Greene and Gilbert,[31] produced unconsciousness in young normal adults by having them rebreathe room air; some subjects lost consciousness when the oxygen concentration fell to 11 per cent, but others were able to tolerate lower concentrations. Lennox and Cobb[55] induced convulsions in epileptics by having them breathe an atmosphere containing 12 per cent oxygen. Levy, Barach, and Bruenn[34] observed pulmonary edema in some subjects with coronary arteriosclerosis who breathed air containing a similar concentration of oxygen. Courville[56] demonstrated microscopic changes in the brain in patients who suffered asphyxia during the induction of nitrous oxide anesthesia. Katz, Hamburger, and Schutz[32] induced unconsciousness in "a few" of their subjects during the induction of anoxemia in a test for angina pectoris. Levy, Bruenn, and Russell[35] caused pulmonary edema in two of their thirty-four patients with coronary heart disease, and two other persons who probably had cerebral arteriosclerosis developed transitory mental confusion. Schneider and Truesdale[54] showed that unconsciousness may develop without adequate warning, even when frequent observations on the blood pressure, heart rate, breathing, and psychic state were made by two trained observers. No untoward effects were experienced by the thirteen subjects studied in the present investigation; the constant, watchful attention of two observers was necessary throughout the test. The possibility of precipitating an attack of angina or pulmonary edema in a patient who may be unable to give adequate warning, together with the lack of evidence of any clear-cut difference between the responses of normals and angina patients in the published reports, as well as in our own studies, have led us to discontinue further tests.

It must be pointed out that the anoxemia tests recorded in the literature and used in the present investigation have varied the duration or the degree of anoxemia (or both) in every subject studied. It is rea-

sonable to believe that an anoxemia test might be of greater value in diagnosis if each subject were subjected to anoxemia of identical duration and degree. It is unlikely, however, that the test will be of diagnostic value even under such conditions, for one of our five angina patients (who did not develop pain) and three of our normal subjects showed electrocardiographic changes after seven minutes of breathing, whereas the remaining four patients with angina developed pain in less than seven minutes, and hence were unable to continue the test for that length of time. It appears probable, therefore, that exposing every subject to an identical anoxemia stimulus would result in false positive or negative reactions and would not be without danger.

It must be concluded that the changes in the electrocardiogram induced by exertion or anoxemia are not of practical value in the diagnosis of coronary artery disease, in spite of the fact that some patients with angina pectoris developed greater electrocardiographic changes than did normal subjects. The accuracy and value of a test for differential diagnosis must be judged not only by the occasional instance in which the result of the test agrees with the facts known about the patient, but also by the number of instances in which the test may give false information. A test which may yield inaccurate information in subjects whose cardiovascular status is known will be of little aid when most needed, namely, when the clinical diagnosis is doubtful.

SUMMARY AND CONCLUSIONS

1. In the present investigation, electrocardiograms were taken *continuously* before, during, and after attacks of angina induced by exercise in twenty patients. Continuous tracings were also taken in five of these patients during generalized anoxemia, which produced pain in four.

2. Changes in the electrocardiogram began long before the onset of the attack, increased until the exercise or anoxemia was discontinued, and then frequently assumed a somewhat different character.

Before and immediately after the onset of angina the most common alteration was a change, usually a depression, in the level of the S-T segment; less frequently there occurred a change in the voltage of the T wave, which only rarely became diphasic or inverted. Changes in the QRS and P waves and the P-R interval were uncommon and usually of slight degree.

Toward the end of the attack, and, also, after the disappearance of pain, the changes in the S-T segment tended to diminish or disappear in most instances, whereas T-wave changes became more pronounced; half of the patients developed diphasic T waves in one or more leads at this time.

3. These changes, especially those in the S-T segment and T wave, were most frequent and most striking in the precordial lead.

4. The changes induced by anoxemia were similar in all respects, except for the heart rate, to those observed in the *same* patients during attacks induced by exercise.

5. The onset of the electrocardiographic changes induced by exertion could be delayed by having the patients breathe oxygen before and during the exercise. This is in accord with the theory that myocardial anoxemia and its sequelae are the cause of anginal pain.

6. Since the changes in the electrocardiogram began before the onset of pain and, in many instances, persisted or increased after the pain subsided, it is obvious that the changes are not characteristic or diagnostic of the attack of pain itself.

7. The abnormalities in the electrocardiogram during and after an attack of angina pectoris following exertion may simulate those which occur in cases of coronary occlusion. To establish the diagnosis of myocardial infarction, therefore, tracings should be taken after the patient has been at rest and has experienced no recent attack of angina.

8. Changes in the electrocardiogram after exertion appear to be of little practical value in the diagnosis of angina pectoris or coronary artery disease, for some subjects without heart disease may show changes similar to those which occur in some patients with angina pectoris, whereas other patients with angina may fail to develop appreciable electrocardiographic changes following the same amount of work.

9. Changes in the electrocardiogram during generalized anoxemia appear to be of little practical value in differential diagnosis, for the difference between the normal and abnormal responses is not sufficiently marked to avoid serious error; also, judging from the literature, the induction of generalized anoxemia is not without danger, especially in patients with arteriosclerosis of the coronary or cerebral vessels.

We wish to express our thanks to the Sanborn Instrument Company for the loan of the vacuum-tube electrocardiograph used in some of these studies.

REFERENCES

1. Riseman, J. E. F., and Brown, M. G.: The Duration of Attacks of Angina Pectoris on Exertion and the Effect of Nitroglycerin and Amyl Nitrite, N. Eng. J. Med. **217**: 470, 1937.
2. Riseman, J. E. F.: The Relation of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris Precipitated by Effort, Am. Heart J. **12**: 53, 1936.
3. Missal, M. E.: Exercise Tests and the Electrocardiograph in the Study of Angina Pectoris, Ann. Int. Med. **11**: 2018, 1938.
4. Bousefield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, The Lancet **11**: 457, 1918.
5. Feil, H., and Siegal, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**: 255, 1928.
6. Hall, D.: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, Lancet **1**: 1254, 1932.
7. Levy, J. R.: Valeur Sémiologique des Altérations du Complexe Ventriculaire Électrique dans les Syndromes Angineux, Arch. des mal. du coeur, des vaisseaux et du sang. **22**: 523, 1929.

8. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris: Their Bearing on the Origin of Anginal Pain, Lancet **1:** 15, 1931.

9. Shapiro, H., and Smyth, L.: Transient Electrocardiographic Changes Noted During Attacks of Angina Pectoris With Report of a Case, J. Lab. and Clin. Med. **23.** 819, 1937-1938.

10. Siegal, M. L., and Feil, H.: Electrokardiographic Studies During Attacks of Angina Pectoris and of Other Paroxysmal Pain, J. Clin. Invest. **10:** 795, 1931.

11. Tiggs, F.: Das Elektrocardiogramm bei Hypoxämie, Ztschr. f. Kreislaufforsch. **28:** 225, 1936.

12. Turner, H. B.: Transient Alterations in the Electrocardiogram During an Attack of Angina Pectoris Terminated by Inhalation of Amyl Nitrite, J. A. M. A. **100:** 38, 1933.

13. Wood, F. C., and Wolferth, C. C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47:** 339, 1931.

14. Bierring, E., Larsen, K., and Nielsen, E.: Some Cases of Slow Pulse Associated With Electrocardiographic Changes in Cardiac Patients After Maximal Work on the Krogh Ergometer, Am. Heart J. **11:** 416, 1936.

15. Burak, M.: Elektrokardiograficzne z obciążeniem w dusznicy bolesnez ze szczególnym uwzględnieniem odprowadzenia czwartego i piątego. (EKG in Patients With Angina Pectoris Before and After Work), Polska Gazeta Lekarska **16:** 233, 1937.

16. Duchosal, P. W., and Henny, G.: Les Modifications de l'Électrocardiogramme après un effort physique. Ont-elles un Interêt Pratique dans le Diagnostic de l'Angine de Poitrine? Arch. du mal. du coeur **30:** 568, 1937.

17. Duchosal, P. W., and Henny, G.: Modifications de l'Électrocardiogramme après l'épreuve d'effort; leur interêt dans les troubles de la circulation coronaire, Helvetica Med. Acta. **3:** 652, 1936.

18. Faliero, A.: Der "Arbeitsversuch" in der electrokardiographischen Diagnose der Angina pectoris. II. Mitteilung, Deutsche Arch. f. klin. Med. **182:** 347, 1932.

19. Goldhammer, St., and Scherf, D.: Elektrokardiographische Untersuchungen bei Kranken mit Angina Pectoris ("Ambulatorischer Typus"), Ztschr. f. klin. Med. **122:** 134, 1932.

20. Katz, L. N., and Landt, H.: The Effect of Standardized Exercise on the Four-lead Electrocardiogram, Am. J. M. Sc. **189:** 346, 1935.

21. Lambert, J.: Les altérations d'origine coronarienne du complex electrocardiographique auriculaire; étude expérimentale et clinique, Arch. du mal. du coeur **30:** 3, 1937.

22. Von Mentzigen, A. F.: Die Bedeutung der Veränderung der Nachschwankung des Elektrokardiogramms nach Belastung für die Beurteilung der Funktion des Herzens, Klin. Wchnschr. **13:** 188, 1934.

23. Motta, G.: Über das thorakale EKG in Ruhe und nach Körperarbeit, Wien. klin. Wchnschr. **50:** 1389, 1937.

24. Puddu, V.: Alterazioni elettrocardiografiche da sforzo, in sogetti normali e anginosi, con particulare riguardo alla derizione toracica, Cardiologia **2:** 183, 1939.

25. Rihl, J., Huttmann, H., and Spiegl, E.: Über das Arbeitselektrokardiogramm, Ztschr. f. Kreislaufforsch. **27:** 19, 1935.

26. Scherf, D.: Zur Frühdiagnose der Angina Pectoris bei der Coronarstenose, Wien. klin. Wchnschr. **49:** 117, 1936.

27. Scherf, D., and Goldhammer, St.: Zur Frühdiagnose der Angina Pectoris, Wien. med. Wchnschr. **83:** 836, 1933.

28. Whitten, M. B., and Herndon, J. H.: Changes in the Electrocardiogram Resulting From Induced Attacks of Angina Pectoris, Am. Heart J. **10:** 392, 1934.
Transactions of American Heart Assoc., 1934.

29. Dietrich, S., and Schwiegk, H.: Das Schmerzproblem der Angina Pectoris, Klin. Wchnschr. **12:** 135, 1933.

30. Graybiel, A., Missiuro, W., Dill, D. B., and Edwards, H. T.: Experimentally Induced Asphyxiation in Cardiac Patients, J. Aviation Med. **8:** 178, 1937.

31. Greene, G. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension: III. Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**: 517, 1921.
32. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, AM. HEART J. **9**: 771, 1934.
33. Larsen, K.: Effect of Anoxemia on the Human Electrocardiogram, Acta Med. Scand. supple. **78**: 141, 1936.
34. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1938.
35. Levy, R. L., Bruenn, H. G., and Russell, N. G.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. M. Sc. **197**: 241, 1939.
36. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing ST Deviation in the Electrocardiogram, AM. HEART J. **8**: 745, 1933.
37. Katz, L. N., Hamburger, W. W., and Lev, M.: The Diagnostic Value of Epinephrine in Angina Pectoris, AM. HEART J. **7**: 371, 1932.
38. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris With Observations on the Electrocardiographic Changes Following Injections of Epinephrine into Normal Subjects and into Patients With Angina Pectoris, Arch. Int. Med. **45**: 191, 1930.
39. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients With Angina Pectoris, Am. J. M. Sc. **188**: 646, 1934.
40. Keefer, C. S., and Resnik, W. H.: Angina Pectoris, Arch. Int. Med. **41**: 769, 1928.
41. Rothschild, M. A., and Kissin, M.: Anginal Syndrome Induced by Gradual General Anoxemia, Proc. Soc. Exper. Biol. and Med. **29**: 577, 1932.
42. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, AM. HEART J. **8**: 1, 1933.
43. Riseman, J. E. F., and Brown, M. G.: The Effect of Oxygen on the Exercise Tolerance of Patients With Angina Pectoris, AM. HEART J. **18**: 150, 1939.
44. Raab, W., and Schönbrunner, E.: Die Normalisierungstendenz des Elektrokardiogramms nebennierenbestrahlter Angina pectoris Kranker, Arch. f. Kreislaufforsch. **4**: 362, 1939.
45. Rosenberger, I.: Über Arbeitsversuche und Elektrokardiogramm, Wien. klin. Wchnschr. **47**: 648, 1934.
46. Einthoven, W.: Weiteres über das Elektrokardiogramm, Pflügers Arch. f. d. ges. Physiol. **122**: 517, 1908.
47. Messerle, N.: Die Veränderungen im Electrokardiogramm bei Körperarbeit, Ztschr. f. d. ges. exper. Med. **60**: 490, 1928.
48. Hoogerwerf, S.: Elektrokardiographische Untersuchungen der Amsterdamer Olympiakämpfer, Arbeitsphysiologie **2**: 61, 1929-1930.
49. Jezierski, W.: Zmiany elektrokardjiografticzne po wysilkach fizycznych. (Changes in the electrocardiogram after exercise [normals]), Polska Gazeta Lekarska, **15**: 677, 1936.
50. Cooper, E. L., O'Sullivan, J., and Hughes, E.: Athletics and the Heart: An Electrocardiographic and Radiological Study of the Response of the Healthy and Diseased Heart to Exercise, Med. J. Australia **1**: 569, 1937.
51. Zettel, H., and Fink, A.: Über Veränderungen im Elektrokardiogramm nach Arbeitsbelastung unter der Schutzmaske, Klin. Wchnschr. **18**: 458, 1939.
52. Bramwell, C., and Ellis, R.: Some Observations on the Circulatory Mechanism in Marathon Runners, Quart. J. Med. **24**: 329, 1930-1931.
53. May, S. H.: Electrocardiographic Response to Gradually Induced Oxygen Deficiency. I. Response of Normal Hearts in Various Age Groups, AM. HEART J. **17**: 655, 1939.
54. Schneider, E. C., and Truesdale, D.: A Study of Low Oxygen Effects During Rebreathing, Am. J. Physiol. **55**: 223, 1921.
55. Lennox, W. C., and Cobb, S.: Epilepsy, Medicine **7**: 105, 1928.
56. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**: 129, 1936.

A STUDY OF THE HYPOTHETIC ANOXEMIC FACTOR IN EXPERIMENTAL AND CLINICAL HYPERTENSION

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THE mechanism of the production of hypertension in dogs by constriction of the renal arteries[1] and the reduction of this experimental hypertension by pexis of the omentum or spleen to the kidney[2] have not been satisfactorily explained. Since ischemia of the kidney is apt to result in anoxia, as well, the degree depending on the reduction of the blood flow and the oxygen consumption of the region affected, a search for a hypothetic anoxemic factor in experimental and clinical hypertension was undertaken. Levy, Light, and Blalock[3] reported a reduction of blood flow and oxygen consumption, with no significant change in the arterial-venous oxygen difference, in the kidney in experimental renal hypertension. It cannot be ascertained from the data presented whether the reduced oxygen consumption was caused by atrophy, or by a decrease in rate of oxygen consumption of the kidney.

The oxygen supply to an organ regulates, in a broad way, the functional activity of the organ, as Barcroft[4] and others have pointed out. The induction of cardiac pain in certain patients with coronary sclerosis by having them inhale oxygen-poor mixtures suggested that anoxia was the critical precipitating factor in the production of anginal pain.[5, 6] Other studies showed that severe cardiac insufficiency, peripheral circulatory failure, and pulmonary edema might be initiated in patients with myocardial disease by the inhalation of oxygen-poor atmospheres.[7, 8]

It has long been known that a transient rise in systolic blood pressure generally follows induced oxygen want, produced either by lowering the pressure or concentration of oxygen in the atmosphere. Furthermore, a lowering of blood pressure in hypertensive patients as a result of oxygen inhalation has been reported. With these facts in mind, the following experiments were undertaken.

Experiment 1.—The effect of continuous inhalation of oxygen-poor mixtures on the blood pressure of dogs in which moderate constriction of the renal arteries had been previously carried out was studied. This degree of constriction had produced only a slight degree of hypertension.

Experiment 2.—The effect of continuous inhalation of 100 per cent oxygen on the blood pressure of dogs in which ischemic renal hypertension had been previously induced was observed.

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Experiment 3.—The effect on the blood pressure of almost continuous inhalation of 100 per cent oxygen in selected cases of hypertensive disease was investigated.

METHODS

A small chamber was constructed in which the desired oxygen concentration could be obtained by regulating the inflow of oxygen and nitrogen. The mixture was analyzed by means of the Orsat-Binger gas analyzer. The technique of Goldblatt[1] was employed in constricting renal arteries in dogs for the production of hypertension.

In the first experiment, two animals with a slight elevation of blood pressure caused by moderate, bilateral, renal artery constriction were kept in the special chamber for seventy-two hours, with the oxygen concentration of the atmosphere maintained at 10 per cent. Blood pressures were measured at 24-hour intervals by the Van Leersum loop method.[9] One of these animals was later kept in the chamber for six hours, with the oxygen concentration maintained at 7 per cent. The blood pressure was measured at the onset and at the end of the experiment.

In the second experiment, two dogs which had been rendered hypertensive by severe bilateral renal artery constriction[1] were placed in the chamber with the oxygen concentration of the atmosphere maintained at approximately 100 per cent for a continuous period of forty-eight hours. Measurements of the blood pressure were made at 24-hour intervals.

In the third experiment, a clinical study, the effect of the almost continuous administration of 100 per cent oxygen, at a rate of 12 L. per min., by means of the "BLB" mask,[10] was studied in three patients with hypertension. The patients, three women, aged 38, 47, and 60 years, respectively, were designated as having mild, moderate, or severe hypertension, depending upon the level of the blood pressure during almost continuous rest in bed. In none of the patients was the hypertension complicated by demonstrable renal or cardiac insufficiency. Patient No. 3, however, had an adenocarcinoma of the thyroid, with no evidence of metastasis, which had been treated by x-radiation. The oxygen was given for seventy-two hours continuously, except during meals and a daily visit to the bathroom.

RESULTS

1. *Effect of Generalized Anoxemia on Blood Pressure of Potentially Hypertensive Dogs.*—Dogs I and II were kept in the animal chamber for seventy-two hours, with the oxygen concentration of the atmosphere maintained at 10 per cent. At this low oxygen concentration, the oxygen saturation of the arterial blood in human subjects falls, within a twenty-minute period, to 65 per cent of normal.[11] Table I records the blood pressure of both animals prior to bilateral, moderate, renal artery constriction, after this procedure, and at 24-hour intervals during the 72-hour period of administration of a mixture containing 10 per cent oxygen. The initial blood pressure of each animal was 130 to 140 mm. Hg; it rose to 175-180 after both renal arteries were clamped. After twenty-four hours in an atmosphere containing 10 per cent oxygen, the blood pressure of Dog I rose from 180 mm. to 200 mm. At forty-eight hours, the blood pressure was 180 mm., and, at seventy-two hours, 190 mm. During the seventy-two hours that Dog II was exposed to an

TABLE I

EFFECT OF GENERALIZED ANOXEMIA (10 PER CENT OXYGEN) ON BLOOD PRESSURE OF POTENTIALLY HYPERTENSIVE DOGS

	BLOOD PRESSURE MM. HG				
	PRIOR TO APPLICATION OF RENAL CLAMPS	AFTER MODERATE CONSTRICTION OF RENAL ARTERIES BY CLAMPS	INHALATION OF 10% OXYGEN		
			24 HR.	48 HR.	72 HR.
Dog I	130	180	200	180	190
Dog II	140	175	165	160	155

atmosphere containing 10 per cent oxygen, a gradual decline in blood pressure, from 170 to 150 mm,, occurred. At a later date, Dog II was subjected to more severe anoxemia, produced by reducing the oxygen concentration of the atmosphere in the chamber to 7 per cent for six hours. Table II records the blood pressure at the onset, and after three and after six hours, and shows a fall from 170 to 140 mm.

2. *Effect of Breathing of 100 Per Cent Oxygen on Blood Pressure of Dogs With Experimental Renal Hypertension.*—Two dogs with experimental renal hypertension were kept in an atmosphere of 100 per cent oxygen for forty-eight hours. From Table III it is seen that the blood pressures of the two animals prior to bilateral, severe, renal artery constriction were 130 and 140 mm. Hg, respectively. Subsequent to this procedure, the blood pressures became stabilized at 230 and 240 mm. After twenty-four hours of breathing 100 per cent oxygen, the blood pressure of the animals remained unchanged. After forty-eight hours the blood pressure of Dog III remained the same. However, Dog IV, after forty-two hours, became distressed, dyspneic, and died. Post-mortem examination, together with microscopic sections, revealed marked edema of the bronchi, resulting in atelectasis.

3. *Effect of Almost Continuous Inhalation of 100 Per Cent Oxygen on the Blood Pressure of Three Patients With Hypertension.*—A summary of the blood pressure readings on the three patients with hypertension during seventy-two hours of almost continuous inhalation of 100 per cent oxygen is given in Table IV. The control range of blood pressure, both during normal breathing of room air and the inhalation of compressed air through the "BLB" mask,[10] was very wide. In patient No. 1 the blood pressure during the control period varied from 154/82 to 180/100, in patient No. 2 from 126/70 to 208/118, and in patient No. 3 from 260/120 to 300/160. During the 72-hour period of oxygen administration the blood pressures of the three patients were comparable to those of the control period. There was neither a lowering nor an elevation of blood pressure during the period of 100 per cent oxygen inhalation.

CONCLUSIONS

The blood pressure of two dogs with hypertension caused by renal ischemia was not influenced by the continuous inhalation of 100 per cent oxygen for twenty-four to forty-eight hours. In three cases of

TABLE II

EFFECT OF SEVERE GENERALIZED ANOXEMIA (7 PER CENT OXYGEN) ON BLOOD PRESSURE OF POTENTIALLY HYPERTENSIVE DOGS

	BLOOD PRESSURE MM. HG			
	PRIOR TO APPLICATION OF RENAL CLAMPS	AFTER MODERATE CONSTRICTION OF RENAL ARTERIES BY CLAMPS	INHALATION OF 7% OXYGEN	
			3 HR.	6 HR.
Dog II	140	170	150	140

TABLE III

EFFECT OF INHALATION OF 100 PER CENT OXYGEN ON BLOOD PRESSURE OF DOGS WITH EXPERIMENTAL HYPERTENSION

	BLOOD PRESSURE MM. HG			
	PRIOR TO APPLICATION OF RENAL CLAMPS	AFTER SEVERE CONSTRICTION OF RENAL ARTERIES BY CLAMPS	INHALATION OF 100% OXYGEN	
			24 HR.	48 HR.
Dog III	170	230	230	230
Dog IV*	140	240	240*	

*Dog died of respiratory distress after forty-three hours in the chamber.

hypertensive disease, the inhalation of 100 per cent oxygen almost continuously for three days did not significantly affect the blood pressure. In two dogs in which partial constriction of the renal arteries had been previously produced, the inhalation of mixtures containing 10 per cent or 7 per cent oxygen did not cause a sustained rise in blood pressure. No evidence could be obtained that a hypothetic anoxemic factor plays a significant role in the pathogenesis of experimental or clinical hypertension. Our results do not, however, exclude the possibility that more severe renal anoxia than we produced might exert an influence on the experimental hypertension produced by constriction of the renal arteries.

TABLE IV

EFFECT OF INHALATION OF 100 PER CENT OXYGEN ON BLOOD PRESSURE OF THREE PATIENTS WITH HYPERTENSION

	BLOOD PRESSURE MM. HG		
	PATIENT 1	PATIENT 2	PATIENT 3
CONTROL RANGE	$\frac{154}{82}$ TO $\frac{180}{100}$	$\frac{126}{70}$ TO $\frac{208}{118}$	$\frac{260}{120}$ TO $\frac{300}{160}$
Hours 1	162/80	136/90	258/124
2	178/94	132/74	268/120
3	168/84	128/78	254/118
4	154/82	142/88	284/138
5	160/90	136/84	292/130
6	170/88	136/84	278/130
12	160/94	140/90	280/135
24	155/88	142/98	282/128
30	174/88	150/92	246/118
36	172/88	132/90	260/130
48	172/90	128/86	280/130
54	154/90	150/90	255/130
60	152/90	155/85	280/135
72	152/90	158/96	300/140

The authors are indebted to Dr. Ernst F. Goldschmidt for assistance in the clinical studies.

REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: The Promotion of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exp. Med. **59**: 347, 1934.
2. Mansfield, J. S., Weeks, D. M., Steiner, A., and Victor, J.: Reduction of Experimental Renal Hypertension by Pexis of Kidney to Omentum or Spleen, Proc. Soc. Exp. Biol. & Med. **40**: 708, 1939.
3. Levy, S. E., Light, R. A., and Blalock, A.: The Blood Flow and Oxygen Consumption of the Kidney in Experimental Renal Hypertension, Am. J. Physiol. **122**: 38, 1938.
4. Barcroft, J.: The Respiratory Function of the Blood, Ed. 2, 1925, Cambridge University Press.
5. Rothchild, M. A., and Kissin, H.: Production of Anginal Syndrome by Induced General Anoxemia, AM. HEART J. **8**: 729, 1933.
6. Keefer, C. S., and Resnik, W. H.: Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**: 769, 1928.
7. Graybiel, A., Missiuro, V., Dill, D. B., and Edwards, H. T.: Experimentally Induced Asphyxiation in Cardiac Patients, With Reference to Certain Hazards in Air Travel and to Use of Asphyxiation as Cardiac Function Test, J. Aviation Med. **8**: 178, 1937.
8. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen-Want in Patients With Cardiac Pain, AM. HEART J. **15**: 187, 1938.
9. Van Leersum, E. C.: Arch. f. d. ges. Physiol. **142**: 377, 1927.
10. Boothby, W. N., Lovelace, W. R., and Bulbulian, A. H.: Design and Construction of the Masks for Oxygen Inhalation Apparatus, Proc. Mayo Cl. **13**: 641, 1938.
11. Barach, A. L.: Unpublished data.

VARIATIONS IN NORMAL PRECORDIAL ELECTROCARDIOGRAMS

A Report of Observations on 100 Normal Subjects

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RECOGNIZING the confusion caused by lack of uniformity in making multiple precordial leads, we made an attempt to ascertain what variations occur in normal individuals. For this study we used one hundred student nurses in the Mercy Hospital School of Nursing. These girls varied in age from 18 to 22 years. All had passed strict physical examinations before entering the school, but before using them we re-examined their hearts in order to exclude any who might have developed cardiac abnormalities since their admission. None with thrills, abnormal impulses, murmurs, split sounds, accentuated sounds, elevated blood pressure, or cardiac enlargement were used. The cardiac silhouette, in each case, was examined under the fluoroscope, and the cardiothoracic ratio determined; at the same time, the outer border of the apex was marked on the chest wall of each girl to assist in placing the electrodes. Corsets and girdles were removed in every case in order to prevent rotation of the heart to the left.

A standard, all-electric electrocardiograph, with string galvanometer, was used. The chest electrode measured 3 cm. in diameter. The tracings were made with the subjects in the sitting position. The terminology recommended by the American Heart Association, namely, CF_1, CF_2, CF_3, CF_4, CF_5, and CF_6, was used. The right arm electrode was placed on the left leg and the left leg electrode was placed in the various positions on the precordium.

The chest electrode was placed as follows: for CF_1, in the fourth intercostal space to the right of the sternum; for CF_2, in the fourth intercostal space to the left of the sternum; for CF_3, at the mid-point of a line drawn from the left margin of the sternum in the fourth intercostal space to the left midclavicular line in the fifth intercostal space; for CF_4, in the left midclavicular line and fifth intercostal space; (NOTE: we fluoroscoped all of our subjects in order that we might use only those in which the outer border of the apex coincided with the junction of the left midclavicular line and the fifth intercostal space); for CF_5, in the left anterior axillary line at the level of the apex; and for CF_6, in the left midaxillary line at the level of the apex.

Measurements of the following deflections were made: P, total QRS, Q, R, S, T, and S-T interval. These measurements are given

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in the accompanying tables. Evidence of slurring and notching was also noted in 22 per cent of the cases. They were found most often on the line connecting the R and S, but occasionally on the upstroke of S. The S-T interval was elevated in 17 per cent, but never more than 2 mm., and then most often in CF_4 and CF_5.

P WAVE	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
-2	3	1	0	0	0	0
-1	61	52	22	10	8	10
0	20	26	59	70	76	76
1	8	14	10	10	6	5
2	2	0	0	0	0	0
Diphasic	6	7	9	8	10	9
TOTAL QRS	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
3	0	0	0	0	1	4
4	0	0	0	0	1	6
5	0	0	0	0	1	1
6	0	0	0	0	0	17
7	0	0	1	3	2	11
8	1	0	0	3	13	11
9	3	0	2	3	8	10
10	1	1	3	6	11	9
11	1	0	4	13	10	16
12	3	1	5	13	11	3
13	3	1	4	11	12	5
14	2	0	2	6	4	2
15	3	1	6	3	4	0
16	8	1	9	5	7	2
17	2	2	6	5	1	1
18	5	2	12	5	3	1
19	3	5	6	4	4	0
20	4	6	8	6	2	0
21	13	11	8	3	1	0
22	11	5	8	2	2	1
23	13	13	4	2	1	0
24	1	6	2	1	0	0
25	4	10	2	2	0	0
26	4	2	1	1	0	0
27	1	5	2	1	0	0
28	3	5	1	0	0	0
29	2	2	0	0	0	0
30	1	6	0	1	0	0
31	4	2	2	1	0	0
32	0	4	2	0	0	0
33	1	1	0	0	0	0
34	2	1	0	0	0	0
35	0	1	0	0	0	0
36	0	1	0	0	0	0
37	1	1	0	0	0	0
38	0	1	0	0	0	0
39	0	0	0	0	0	0
40	0	3	0	0	0	0
R WAVE	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
0	4	0	0	0	0	1
1	6	3	2	1	0	1
2	30	9	4	4	3	7
3	26	10	19	6	5	8
4	17	12	18	18	8	9
5	7	24	22	13	8	10
6	6	22	21	13	20	22
7	4	8	5	14	17	17

R WAVE	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
8	0	3	4	14	11	5
9	0	2	2	2	9	4
10	0	3	2	3	2	7
11	0	2	0	3	4	1
12	0	1	1	4	4	3
13	0	1	0	2	2	1
14	0	0	0	2	0	2
15	0	0	0	0	2	1
16	0	0	0	0	2	0
17	0	0	0	0	1	0
18	0	0	0	1	0	0
19	0	0	0	0	1	0
20	0	0	0	0	1	0
21	0	0	0	0	0	1
S WAVE	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
0	0	0	0	2	13	33
1	0	0	0	2	4	15
2	0	0	0	3	17	18
3	0	0	0	6	10	17
4	0	0	1	8	17	5
5	0	0	1	7	17	1
6	0	0	2	15	4	6
7	2	0	5	16	3	3
8	1	0	4	2	1	2
9	4	1	6	2	1	0
10	5	2	8	6	5	0
11	1	0	6	2	3	0
12	7	2	11	8	2	0
13	3	4	13	8	0	0
14	3	0	12	2	3	0
15	7	3	4	0	0	0
16	4	5	5	2	0	0
17	6	7	6	4	0	0
18	14	7	2	1	0	0
19	10	11	4	2	0	0
20	9	12	2	0	0	0
21	2	4	1	0	0	0
22	5	13	2	0	0	0
23	5	1	2	1	0	0
24	3	5	1	0	0	0
25	3	7	0	0	0	0
26	2	4	1	0	0	0
27	2	3	0	0	0	0
28	0	4	0	0	0	0
29	1	1	1	0	0	0
30	2	3	0	0	0	0
31	0	1	0	0	0	0
T WAVE	CF_1	CF_2	CF_3	CF_4	CF_5	CF_6
-6	1	0	0	0	0	0
-5	0	0	0	0	0	0
-4	0	0	0	0	0	0
-3	12	0	0	0	0	0
-2	29	1	0	0	0	0
-1	29	5	1	1	0	0
0	8	3	1	0	0	2
1	14	29	12	7	8	29
2	7	28	32	25	34	45
3	0	20	31	23	26	17
4	0	10	11	27	21	6
5	0	2	9	9	8	2
6	0	0	1	4	3	0
7	1	1	2	4	0	0

An inspection of these charts shows that the initial deflection of QRS is upward, and that the T waves are upright, in nearly all leads, which is the exact opposite of what was found with the old method of making chest leads. The characteristics of each lead were as follows:

LEAD CF_1.—The P wave varied in amplitude from –2 to +2 mm.; in 61 per cent of the cases it measured –1 mm., and was absent or isoelectric in 20 per cent. The total QRS varied from 8 to 37 mm.; 35 per cent fell between 21 and 23 mm. There were no Q waves. The R wave measured from 4 to 7 mm.; 30 per cent were 2 mm., and 26 per cent 3 mm., tall. The S wave showed a depth of 2 to 30 mm.; 39 per cent were between 17 and 21 mm. The T waves ranged from –6 to +7 mm.; 70 per cent were negative by 1 to 3 mm.

LEAD CF_2.—The P wave tended to be negative; 52 per cent were –1 mm., and 25 per cent isoelectric. The total QRS varied from 10 to 40 mm.; 45 per cent were between 21 and 25 mm. The R wave showed about the same variation as in CF_1; 68 per cent measured from 3 to 6 mm. S was slightly deeper; 40 per cent had an amplitude of from –19 to +22 mm. T became positive; it was negative in only 6 per cent of cases, and in 80 per cent had an amplitude of 1 to 4 mm.

LEAD CF_3.—The P wave tended to lose its negativity; it was diphasic in 58 per cent of the cases, and its amplitude varied from –1 to +1 mm. The amplitude of the total QRS was slightly less than in the preceding leads; it varied from 7 to 32 mm., and 63 per cent measured from 15 to 22 mm. The R wave became somewhat taller, ranging from 1 to 12 mm.; 80 per cent measured from 3 to 6 mm. The S wave became smaller; its least amplitude was –4 mm., and its greatest –29 mm., with 36 per cent measuring from –12 to –14 mm. The T wave lost its negative characteristic in all except one case, in which it was –1 mm.; 86 per cent varied within 1 to 4 mm.

LEAD CF_4.—This lead corresponds to the apex lead. The P waves were essentially as in the preceding leads, except that fewer showed negativity; 10 per cent were –1, 70 per cent isoelectric, 8 per cent diphasic, and 10 per cent 1 mm. tall. Total QRS became smaller; 37 per cent varied from 11 to 13 mm., and the total variation was 7 to 31 mm. Only one Q wave was seen, and it was less than 1 mm. deep. The R wave varied from 1 to 18 mm.; 72 per cent of the variations fell within 4 to 8 mm. The S wave varied from 0 to 23 mm., with 31 per cent measuring 6 to 7 mm. The T wave varied 2 to 4 mm. in 75 per cent of the cases, with a total variation of from –1 to +7 mm.

LEAD CF_5.—The P wave was essentially as in CF_4. Total QRS varied from 3 to 23 mm., with 65 per cent measuring 8 to 13 mm. R became slightly taller and S less deep; 78 per cent were 5 mm. or less. T completely lost its negative and diphasic characteristics; it measured from 1 to 6 mm., with 81 per cent lying between 1 and 4 mm. A Q wave appeared in 20 per cent of the cases, and all were 2 mm. or less.

LEAD CF_6.—P was the same as in CF_4 and CF_5, with a variation from −1 to +1 mm.; most of the P waves (76 per cent) were isoelectric. Total QRS did not exceed 22 mm., and that in only one instance; 74 per cent measured 5 to 10 mm. R was about the same as in CF_5. S was absent in 33 per cent of the cases; 50 per cent measured 1 to 3 mm. T was isoelectric in two cases and measured 1 to 3 mm. in 90 per cent of the cases, but did not exceed 5 mm. in any case. A Q wave was found in 33 per cent of cases, but never measured more than −2 mm.

For the sake of completeness the following brief discussion of the limb leads is included: No rhythm other than normal sinus and occasional sinus arrhythmia was noted. The longest P-R interval was 0.2 second (one case), and the shortest was 0.12 second. There was one case in which left axis deviation was noted, and that by only 2 mm.; five subjects showed right axis deviation—two of 1 mm., two of 2 mm., and one of 3 mm. Q waves appeared seventy-three times, as follows: three of 1 mm. depth, three of 2 mm., and one of 3 mm. in Lead I; in Lead II there were seventeen of 1 mm., and nine of 2 mm.; whereas in Lead III, twenty-four were 1 mm. in depth, eleven, 2 mm., and five, 3 mm. The R waves were normal in amplitude in all cases except as noted above in the discussion of axis deviation. No splintering or apex slurring was noted; occasional slurring was seen at the base. The S-T segment was never more than 1 mm. from the isoelectric line. The T-wave changes included thirteen flat in Lead III, six diphasic in Lead III, and twenty-four inverted in Lead III. One subject had a T_1 2 mm. tall, a diphasic T_2, and T_3 inversion of 1 mm.

Referring again to the chest leads, there was one observation which I would like to make in reference to the T waves. In positions CF_3, CF_4, and CF_5, one subject had a flat T in CF_3, and twelve had a 1 mm. T in CF_3, seven in CF_4, and eight in CF_5. In two of these cases T_3 was upright, whereas all other T waves in Lead III were flat or inverted. It does not follow, however, that flat or inverted T waves in the Lead III mean that there will be depression in the positions around CF_4, because a number of the subjects with T_3 inversion had T waves in CF_3 to CF_5 as tall as 5 mm. As a matter of fact, in the one case in which T was inverted in CF_4, the complexes in the limb leads were entirely normal.

SUMMARY

1. One hundred student nurses without demonstrable heart disease were studied in order to set up normal standards for use in precordial electrocardiography.

2. The technique followed was that recommended by the Joint Committee of The American Heart Association and the Cardiac Society of Great Britain and Ireland.

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1. One hundred student nurses without demonstrable heart disease were studied in order to set up normal standards for use in precordial electrocardiography.

2. The technique followed was that recommended by the Joint Committee of The American Heart Association and the Cardiac Society of Great Britain and Ireland.

3. The right arm electrode was placed on the left leg, and the left leg electrode was placed on the precordium; this method conforms with the CF nomenclature.

CONCLUSIONS

1. P waves were largely negative or isoelectric; when positive, the amplitude did not exceed 1 mm.

2. Total QRS varied within wide limits, but became smaller as the electrode was moved from right to left.

3. Q waves appeared in 20 per cent of cases in CF_5 and CF_6, but never measured more than 3 mm.

4. R waves showed wide variations, up to 21 mm., but in all leads the greater number measured from 3 to 7 mm.

5. S waves became smaller as the electrode was moved from right to left; the greatest number averaged 18 to 19 mm. in CF_1, and varied from being isoelectric to a height of 3 mm. in CF_6.

6. The T waves were usually negative in Lead CF_1; 70 per cent measured –1 to –3 mm., but they became upright in CF_2 and maintained the same average height of 2 to 4 mm. in all leads.

7. No definite relation could be shown between limb-lead T waves and chest-lead T waves in the positions around CF_4; although there were many flat or inverted T waves in the limb leads when the T waves in the chest leads were depressed, many subjects who showed T_3 inversion had tall, upright T waves in CF_3 to CF_5.

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STUDIES ON CORONARY OCCLUSION

I. The Effects on the Electrocardiogram of the Cat of Producing Anoxemia After Coronary Artery Ligation

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During attacks of angina pectoris and after coronary occlusion, the electrocardiographic changes, as well as the associated pain, are believed to result from anoxia of a portion of cardiac muscle, caused in both instances by myocardial ischemia. Severe experimental anoxemia may result in electrocardiographic changes similar to those accompanying impairment of coronary blood flow. Several weeks after coronary artery ligation in cats, the electrocardiogram may approach or return to normal, despite post-mortem evidence of persistent myocardial damage. The infarct is surrounded by an area of relatively ischemic cardiac muscle. In such cases, experimentally induced anoxemia may exaggerate the local ischemic anoxia sufficiently to affect the electrocardiogram.

In the course of some experiments involving coronary ligation in cats, it was found that the electrocardiographic changes following the ligation frequently did not persist for more than two or three weeks. Autopsy revealed that this improvement in the electrocardiogram was not caused by the disappearance of the infarct. Since the electrocardiogram, the sedimentation rate, and the leucocyte count had returned to normal at this time, it became necessary to find some other means of detecting the presence of myocardial damage.

In normal cats, the anoxemia which results from the administration of an atmosphere containing 10 per cent oxygen caused no alteration in the electrocardiogram. On the other hand, after coronary artery ligation the same degree of anoxemia produced sufficient myocardial anoxia to alter the electrocardiogram. Since Levy, et al.,[1] have advocated a similar procedure for the testing of patients suspected of having coronary insufficiency, the results obtained with cats attain clinical significance.

REVIEW OF THE LITERATURE

Many studies have been made of the effects of either anoxemia or coronary artery ligation on the form of the electrocardiogram. A preliminary report has already been made[2] on the effects of combined anoxemia and ligation. It is not necessary to reiterate an analysis of the reported work on coronary ligation.[3, 4] A brief reference to the

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effects of anoxemia on the electrocardiogram of the normal animal is appended for comparison with our results.

Katz, Hamburger, and Schutz[5] and Katz and Hamburger[6] showed that the anoxemia induced in normal subjects by the use of a rebreathing spirometer, with absorption of carbon dioxide, resulted in diminished amplitude and, occasionally, in inversion of the T waves and depression of the RS-T segments. These electrocardiographic changes were not accompanied by pain, and disappeared when air was breathed again. Ward and Wright[7] showed that the anoxemia of nitrous oxide anesthesia caused tachycardia, and reduction, abolition, or inversion of T_2. In a case of carbon monoxide poisoning reported by Colvin,[8] there was T-wave inversion in all leads, with a return to normal in thirteen days. Haggard,[9] in studying experimental carbon monoxide asphyxia, found that the oxygen deficiency did not impair auriculoventricular conduction until respiratory failure supervened, after which there was heart block which was probably caused by anoxemia, since the change was reversible.

Rothschild and Kissin,[10] using the rebreathing method with removal of carbon dioxide, precipitated attacks of cardiac pain in eighteen of twenty-six angina patients, but in none of twenty controls. Pain occurred at levels of oxygen tension varying from 5.9 to 11.2 per cent. However, these authors[11] could demonstrate no electrocardiographic changes which would distinguish between normal subjects and those with coronary insufficiency. Both groups showed identical changes, i.e., S-T deviation, usually depression, which seemed to be related to the degree of anoxemia. Bergman[12] demonstrated that high altitude may cause pain in patients subject to angina pectoris, but had no effect on normal subjects. He stated that the administration of oxygen relieved the anginal pain which occurred in the rarefied atmosphere of airplane travel.

Anoxemia induced by the administration of an atmosphere containing 12 per cent oxygen to patients with coronary insufficiency has been found to cause pain and to induce reversible electrocardiographic changes similar to those which follow coronary occlusion.[13] The responses to the anoxemia were inconstant; pain occurred in the same patients at various levels of arterial oxygen saturation. Many patients experienced no pain. The electrocardiogram showed changes in amplitude or direction of all T waves and depression of many RS-T segments. The heart rate was usually increased. Only minor electrocardiographic changes occurred in the normal subjects, i.e., slight flattening of the T waves and slight RS-T depression. Levy, Barach, and Bruenn[13] concluded that the electrocardiographic changes were not specific, since they also occurred in such conditions as anemia and uremia. In a further series[1] of patients with coronary insufficiency, anoxemia was induced by the administration of an atmosphere con-

taining 10 per cent oxygen. This resulted in electrocardiographic changes which did not occur in normal subjects. The changes appeared with sufficiently great regularity to warrant the use of this procedure as a clinical test for coronary insufficiency.

A considerable amount of experimental work has been done on the effects of anoxemia[14-18] and asphyxia[16, 19, 20] on the dog's electrocardiogram. With slight degrees of anoxemia the principal electrocardiographic changes were tachycardia, flattening or inversion of the T waves with increased negativity of already inverted T waves, or increased amplitude of T waves. With greater oxygen unsaturation[15] (partial pressure of 18 to 22 mm. Hg) the amplitude of the T waves increased tremendously, and the RS-T segments became elevated. Kountz and Gruber[18] reported that similar changes occurred when the oxygen saturation of arterial blood fell below 50 per cent. With more marked unsaturation there were disappearance of P waves, descending displacement of the pacemaker with supervention of nodal rhythm, and auriculoventricular dissociation. All of these changes were abolished by breathing oxygen or air, provided this was started before the onset of respiratory failure.

A long-term experimental study of the effects of anoxemia on the electrocardiogram of the cat before and after coronary ligation was undertaken in the hope that it would aid in the elucidation of the subject.

METHOD

Male and nonpregnant female cats weighing over 2.5 kg. were used in this study. With a few exceptions, to be noted later, the following procedure was employed. The cats were anesthetized by the intraperitoneal administration of sodium pentobarbital (30 mg. per kg.). After induction of the anesthesia the head of the cat was inserted into an airtight mask connected with a 150 liter spirometer which contained either 10 per cent or 5 per cent oxygen in nitrogen. Rebreathing was prevented by a double flutter-valve in the mask. A large two-way valve between spirometer and mask made possible an instantaneous change from room air to spirometer contents, and back to air, without removal of the mask.

Standard three-lead electrocardiograms were taken with the animal lying on its right side. After a control electrocardiogram, the gases breathed by the cat were changed from room air to the low oxygen mixture in the spirometer. Electrocardiograms were taken five and twenty minutes later, after which the breathing of room air was reinstituted, and ten minutes later a fourth electrocardiogram was made. This procedure was repeated after the coronary artery ligation, and subsequently at about weekly intervals. Electrocardiograms were also taken on the unanesthetized cats before operation, in order to ascertain whether any changes were induced by the barbiturate anesthesia.

Leucocyte counts and erythrocyte sedimentation rates were done on all of the cats, but, since they have no immediate bearing on the observations presented here, they are not included in the report.

Operation.—Under sodium pentobarbital anesthesia, occasionally supplemented by ether, a soft rubber catheter was passed transorally into the trachea for the administration of artificial respiration by intermittent positive pressure insufflation.

The operations were performed under aseptic conditions. A 4 cm. incision was made in the fourth or fifth intercostal space, extending laterally from the left sternal border. The parietal pleura was exposed by blunt dissection and incised. The pericardium was opened longitudinally to expose the anterior surface of the left ventricle. The left anterior descending coronary artery was visualized, and its left branch ligated at a point close to its origin. In every instance this was followed by cyanosis of a wedge-shaped area of heart muscle distal to the ligature. There was transient, widespread ventricular fibrillation in a few cases. The pericardial sac and the chest were closed by silk sutures, and the wound was dressed with gauze-collodion. Skin sutures were removed on or about the seventh postoperative day. The operations required fifteen to twenty minutes. There was no operative mortality. Approximately one hour after the operation, and before recovery from anesthesia, the cats were given, by stomach tube, 75 c.c. of 5 per cent dextrose in normal saline solution. They were fed canned salmon after the first postoperative day.

The cats were killed by the intravenous injection of chloroform at intervals varying from two weeks to two months after operation, and autopsies were performed. The cardiac infarcts were delineated and contact tracings made. These were measured with a planimeter (Fig. 3). Serial sections of the infarcted area of several hearts were made, but, since this study afforded no additional information, it was discontinued.

RESULTS

Postoperative Course.—The cats showed little disability as a result of the operation; most of them ate normally the next day, or shortly thereafter. There were a few superficial wound infections, which cleared up rapidly. Cat No. 25 developed a right subpectoral abscess, and was sacrificed on the fourteenth postoperative day. No connection with the operative site could be demonstrated at autopsy.

Seven cats developed "snuffles" and died of inanition. Three of these died during experimental anoxemia; death was apparently caused by respiratory, rather than cardiac, failure. One of the cats developed complete heart block after breathing a mixture containing 10 per cent oxygen for five minutes, and died ten minutes later, despite having been returned to air. Two other cats were sacrificed because of impending death from "snuffles."

The remaining ten cats were sacrificed at intervals of approximately four, six, and eight weeks after operation. In all cases autopsy revealed pleuropericardial adhesions, and adhesion of the parietal to the visceral pericardium over the area of infarction. As shown in Fig. 3, there was great variation in the areas of the infarcts. These infarcts were sharply delineable from the adjacent myocardium.

Cat No. 21 showed only traces of infarction. Its electrocardiogram had returned to normal by the fourteenth postoperative day, and two weeks after this the induction of anoxemia resulted in no electrocardiographic changes.

No attempt was made to correlate the size of infarct with the weight of the heart or of the cat, since Gold, Travell, and Modell[21] could establish no definite relationship between them.

Effect of Sodium Pentobarbital Anesthesia on the Electrocardiogram.—Hafkesbring and MacCalmont[22] reported upon sodium pentobarbital, sodium barbital, and sodium amytal anesthesia in dogs and cats. With all three drugs there was a tendency to T-wave reversal. Kohn and Lederer[23] described the changes produced by pentothal and evipal on the electrocardiograms of dogs, cats, rabbits, and monkeys. Many of the animals showed no significant changes. Others developed ectopic beats, alternating normal and premature rhythms, and disturbances in intraventricular conduction. The P-R interval was sometimes shortened, and occasionally there was T-wave depression. Volpitto and Marangoni,[24] on the other hand, reported that pentothal, evipal, and sodium isoamyl-ethyl-thiobarbiturate anesthesia did not cause any changes in the electrocardiogram in seventeen clinical trials.

In the present work, the question whether or not any significant electrocardiographic changes were induced by the anesthesia is relatively unimportant, since all comparative observations were made with the cats anesthetized with sodium pentobarbital. However, control electrocardiograms were made on ten cats before and after the induction of anesthesia with sodium pentobarbital (30 mg. per kg. intraperitoneally). The changes observed are summarized below:

1. Rate—One cat showed a decrease, three no change, and six an increase.

2. RS-T segment—Seven cats showed no change. Two cats showed depression, and one an elevation, in Lead II.

3. T waves—Nine cats showed changes in one or more leads. There was increased amplitude of T_1 in four cats. Seven cats showed T_2 changes, five a decrease, and two an increase, in amplitude. Seven cats had T_3 changes, four showing inversion and three increased amplitude.

4. There were no changes in rhythm or conduction.

These observations, in general, are in conformity with the results of other workers.

In order to ascertain the effect of repeated anesthetizations upon the electrocardiogram of normal cats, as well as to establish more precisely the effect of varying the depth of anesthesia, the following experiment was performed. Five normal cats were given sodium pentobarbital intraperitoneally at weekly intervals. Each cat received 3 doses of 30 mg., and one dose of 40 mg., 50 mg., and 60 mg. per kg., respectively, on the separate experimental days. These cats were not used further. The results are summarized below:

1. Rate—There was no constant effect with increased depth of anesthesia.

2. RS-T segment—One cat showed elevation in all leads at one time or another, but not in proportion to the depth of anesthesia.

3. T waves—There was no relationship of depth of anesthesia to contour or amplitude.

Evidently, the animals respond to repeated anesthetizations in much the same manner. The effects of deep anesthesia do not differ from those of light anesthesia.

Effects of Anoxemia on the Electrocardiogram in Cats Which Had Not Been Operated on.—Electrocardiograms were taken on twelve anesthetized cats which had not been operated on, before and during the inhalation of a mixture containing 10 per cent oxygen. The heart rate varied considerably in the different cats, probably because barbiturates produce a partial peripheral vagus paralysis.[25] The cardiac acceleration anticipated from the induced anoxemia was conceivably masked by acceleration caused by the anesthetic. Four of the cats showed variable changes in the amplitude of the T waves, but no cat showed RS-T segment deviation or changes in rhythm or conduction. Three of the cats were studied a second time, using 5 per cent oxygen to induce a greater degree of anoxemia. Inversion of the T waves occurred in all leads, but again there were no changes in the RS-T segment, in rhythm, or in conduction. However, since later studies showed that the administration of an atmosphere containing 10 per cent oxygen did induce characteristic electrocardiographic changes in cats which had been operated on, it was deemed unnecessary to increase the anoxemia further, except in a few selected cases to be described.

Effects of Coronary Artery Ligation on the Electrocardiogram.—There is a voluminous literature on the form of the electrocardiogram following coronary artery ligation in dogs,[26-28] but there is much less on the changes in cats.[21] The principal changes which are reported to follow ligation of the left anterior descending coronary artery are an upward deviation of the RS-T segment in Lead I and a downward displacement in Leads II and III. A temporary increase in the amplitude of the T waves, with subsequent inversion and assumption of the isoelectric position, was common. In many instances, however, large infarcts did not produce any changes in the RS-T segment.

In the present series of cats the electrocardiographic changes following coronary artery ligation were, on the whole, in conformity with those observed by previous investigators. All but three of the fourteen cats showed upward displacement of the RS-T segment in at least two leads. Two cats showed upward displacement in Lead I, with downward displacement in the other two leads. One cat showed no change until after several days had elapsed. The T waves in Leads II and III were, with very few exceptions, increased in amplitude. T_1 was not uniformly altered. Contrary to previous reports, no changes in rhythm or conduction were found.

Effects of Anoxemia on the Electrocardiogram After Operation.—Electrocardiograms were taken immediately after operation, then at

about weekly intervals for the first month, and subsequently at bi-weekly intervals before, during, and after recovery from induced anoxemia.

Usually, after coronary artery ligation, electrocardiographic changes were produced by the administration of a mixture containing 10 per cent oxygen. Only two of fourteen cats failed to show changes during the period of anoxemia. The changes were fairly consistent during the postoperative life span of each individual animal, although they were not always the same in different cats. This variation in response to anoxemia is in keeping with the observation that the electrocardiographic changes after coronary artery ligation are not always identical. Because they were found to be not significantly changed, the P-R interval, the height of the P wave, the intraventricular conduction time, the voltage, and the electrical axis, as well as the presence of Q waves, are not given formal mention.

Immediately following the ligation, as shown in Table I, inhalation of an atmosphere containing 10 per cent oxygen caused an increase in the deviation of the RS-T segment in most of the electrocardiograms in which a deviation had been produced by the ligation. In a few instances, isoelectric RS-T segments were displaced as a result of the anoxemia. The occasional T-wave changes were slight and variable. All of these alterations which were induced by the anoxemia disappeared after ten minutes of air breathing.

TABLE I

THE EFFECT OF ANOXEMIA ON THE ELECTROCARDIOGRAM WHICH WAS TAKEN IMMEDIATELY AFTER OPERATION

CAT NO.	BEFORE INDUCTION OF ANOXEMIA			DURING ANOXEMIA INDUCED BY THE INHALATION OF AN ATMOSPHERE CONTAINING 10 PER CENT OXYGEN		
	RS-T_1	RS-T_2	RS-T_3	RS-T_1	RS-T_2	RS-T_3
21	0.5 ↑	0.5 ↑	< 0.5 ↑	0.5 ↑	1.0 ↑	0
22*	0.5 ↑	2.0 ↑	1.5 ↑	0.5 ↑	2.5 ↑	2.0 ↑
24	0	1.5 ↑	1.0 ↑	0	2.0 ↑	1.5 ↑
25	2.5 ↑	1.0 ↓	4.0 ↓	4.0 ↑	1.0 ↓	6.5 ↓
26	0	0	0	< 0.5 ↑	< 0.5 ↑	0
27	1.0 ↑	1.0 ↑	< 0.5 ↑	0.5 ↑	0.5 ↑	0
28*	1.0 ↑	3.5 ↑	2.0 ↑	1.5 ↑	5.0 ↑	3.0 ↑
29	0	3.0 ↑	3.0 ↑	1.0 ↑	4.0 ↓	3.0 ↑

Arrows indicate direction of deviation of the RS-T segment from its level in the preoperative control tracings; numbers denote millimeters of deviation.

Preoperative control observations showed no RS-T segment deviation in any cat during the anoxemic state.

*See Figs. 1 and 2.

During the postoperative period the RS-T segments approached the isoelectric line, and the T waves approached the preoperative configuration. One week after ligation, all of the tracings still showed "coronary" changes, but these were less extensive than at first. At this time, anoxemia resulted in electrocardiographic changes which closely resembled those induced by anoxemia immediately after the

operation. The second- and third-week observations resembled the first, in that anoxemia exaggerated the RS-T segment deviations. The electrocardiograms of ten of fourteen cats returned to normal in an average of twenty days (12 to 32). In nine of these, deviations in the RS-T segment similar to those in the postoperative electrocardiograms were evoked by the induction of anoxemia (Table II). These changes disappeared when the animals were allowed to breathe air. In those cats whose electrocardiograms failed to return completely to normal, anoxemia increased the RS-T deviation and evoked it in those leads from which it had disappeared. T_1 changes continued to be infrequent and variable. The electrocardiograms of two other cats which had been operated on (No. 11 and 14) returned to normal. However, these cats were ill; they died shortly after the administration of an atmosphere containing 10 per cent oxygen and were not included in Table II. The tracings showed frequent ventricular premature contractions, followed by complete heart block.

TABLE II

THE EFFECT OF INDUCED ANOXEMIA ON THE ELECTROCARDIOGRAM AFTER IT RETURNED TO NORMAL FOLLOWING CORONARY ARTERY LIGATION
(TEN OF FOURTEEN CATS)

CAT NO.	RETURN TO NORMAL	EFFECT OF ANOXEMIA ON ELECTROCARDIOGRAM			
	DAYS	DAY OF ECG	RS-T_1	RS-T_2	RS-T_3
7	21	33	0.5 ↑	0.5 ↑	0
9	23	35	0.5 ↑	1.0 ↑	0.5 ↑
12	29	29	0	0	0
19	32	32	< 0.5 ↓	0.5 ↓	0
21	12	20	0	0.5 ↑	0
22	29	47	0	1.0 ↑	0.5 ↑
24	20	30	0.5 ↑	0.5 ↑	0.5 ↑
26	15	22	< 0.5 ↓	0	1.0 ↓
27	21	21	0.5 ↓	0	0
29	24	24	0.5 ↑	1.0 ↑	1.0 ↑

Arrows indicate direction of deviation of the RS-T segment from the level during air breathing; numbers denote millimeters of deviation.

Of four cats which showed electrocardiographic changes after ligation, two (No. 12 and 16) showed no exaggeration of the RS-T deviation as a result of anoxemia, which was induced but once, and by an atmosphere containing 10 per cent oxygen. An oxygen-poor mixture (10 per cent) no longer evoked any electrocardiographic response on the sixty-eighth and twenty-ninth days after operation in the other two. Breathing a mixture containing five per cent oxygen induced electrocardiographic changes in one, but failed in the other (No. 21), which showed only a trace of infarction at autopsy (page 722). The administration of a mixture containing 5 per cent oxygen to two other cats induced electrocardiographic changes qualitatively similar to those caused by the administration of an atmosphere containing 10 per cent oxygen. These cats also showed the usual T-wave inversion

which occurred when a mixture containing 5 per cent oxygen was administered to the control cats.

Pericardiotomy, without coronary artery ligation, was performed on one cat. In this case, the administration of an oxygen-poor mixture (10 per cent) produced no RS-T changes at any time during the first four postoperative weeks.

To ascertain whether the changes observed after the induction of anoxemia were caused by alterations in blood pressure, experiments were made upon six additional animals, three of which were normal. The blood pressure was recorded from one of the carotid arteries, and was progressively lowered by phlebotomy. Electrocardiograms were taken at various intervals as the blood pressure fell from an average

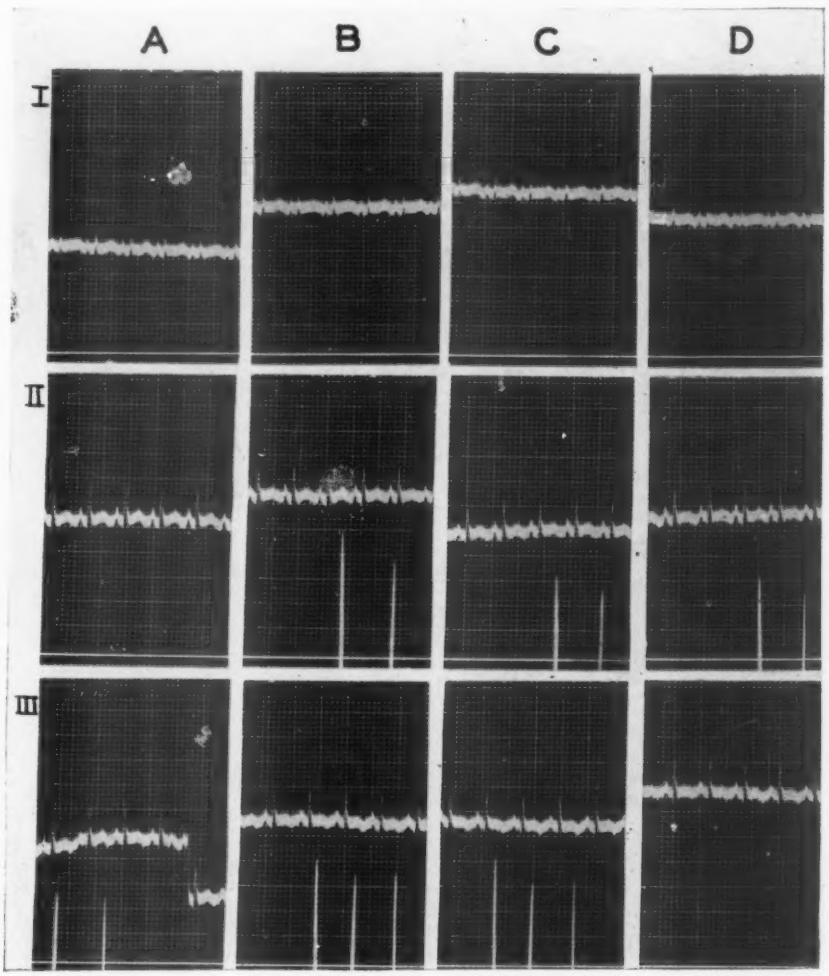

Fig. 1(*a*).—Cat No. 22, preoperative control electrocardiograms. *A*. While breathing air. *B*. After five minutes of a mixture containing 10 per cent oxygen. *C*. After twenty minutes of a mixture containing 10 per cent oxygen. *D*. After ten minutes recovery period of air breathing.

normal of 130 mm. Hg to zero. Three of these cats had had coronary artery ligations three to four months previously, and on these cats anoxemia was induced when the blood pressure had been reduced to about 80 mm., and again at 40 mm. Hg. In these three cats, lowering of the blood pressure did not alter the effect of anoxemia on the electrocardiogram, and in all six cats the form of the electrocardiogram was unaltered until the blood pressure had fallen to 10 mm. Hg, when some RS-T abnormalities appeared.

The blood pressure was either unchanged or raised slightly by the induction of anoxemia in five cats. The sixth cat showed a fall in blood pressure.

The blood pressure was recorded upon two cats during the performance of the ligation operation. While the chest was open there

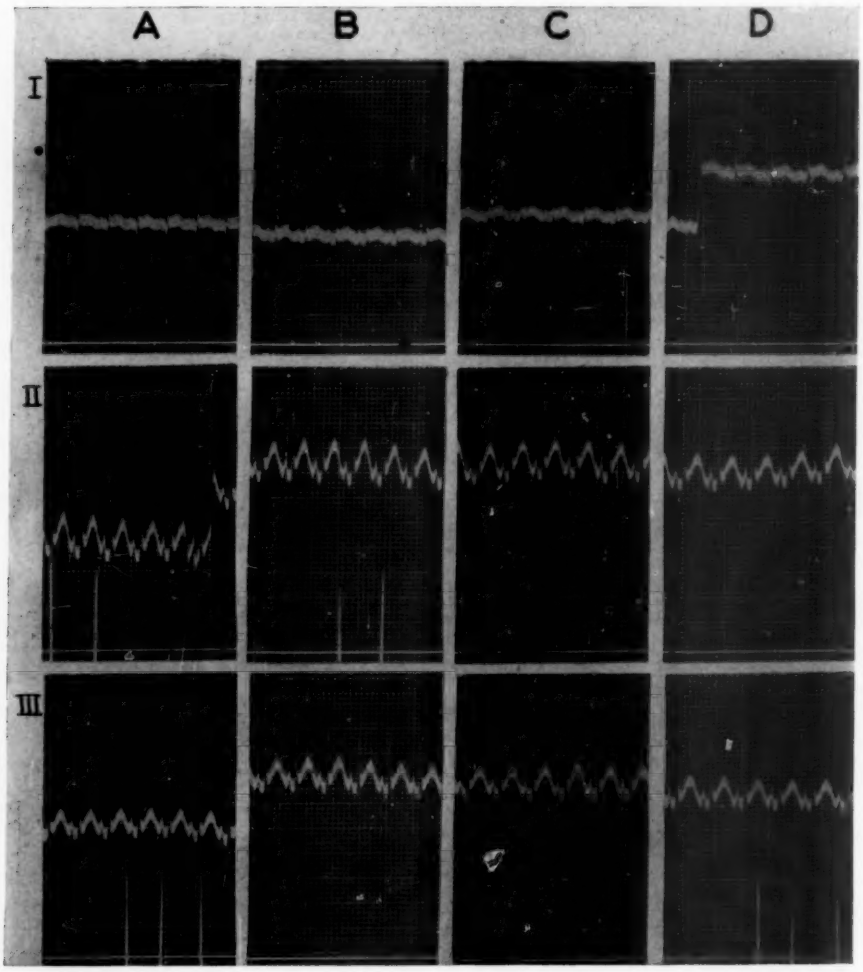

Fig. 1(*b*).—Cat No. 22, electrocardiograms taken immediately after operation. (Legend as in Fig. 1 (*a*).)

was a profound fall in blood pressure, which promptly recovered, upon closure of the chest, to within 10 to 20 mm. Hg of the preoperative level. In one cat upon which only pericardiotomy was performed, without coronary artery ligation, the blood pressure returned to normal upon closure of the chest.

The drop in percentage oxygen saturation of the arterial blood which resulted from the administration of an atmosphere containing 10 per cent oxygen for 15 minutes was determined by the method of Van Slyke and Neill[29] in two cats. In one there was a drop from 88 per cent to 44 per cent, and, in the other, from 84 per cent to 57 per cent. The low initial figures were probably caused by the respiratory depression resulting from the anesthesia.

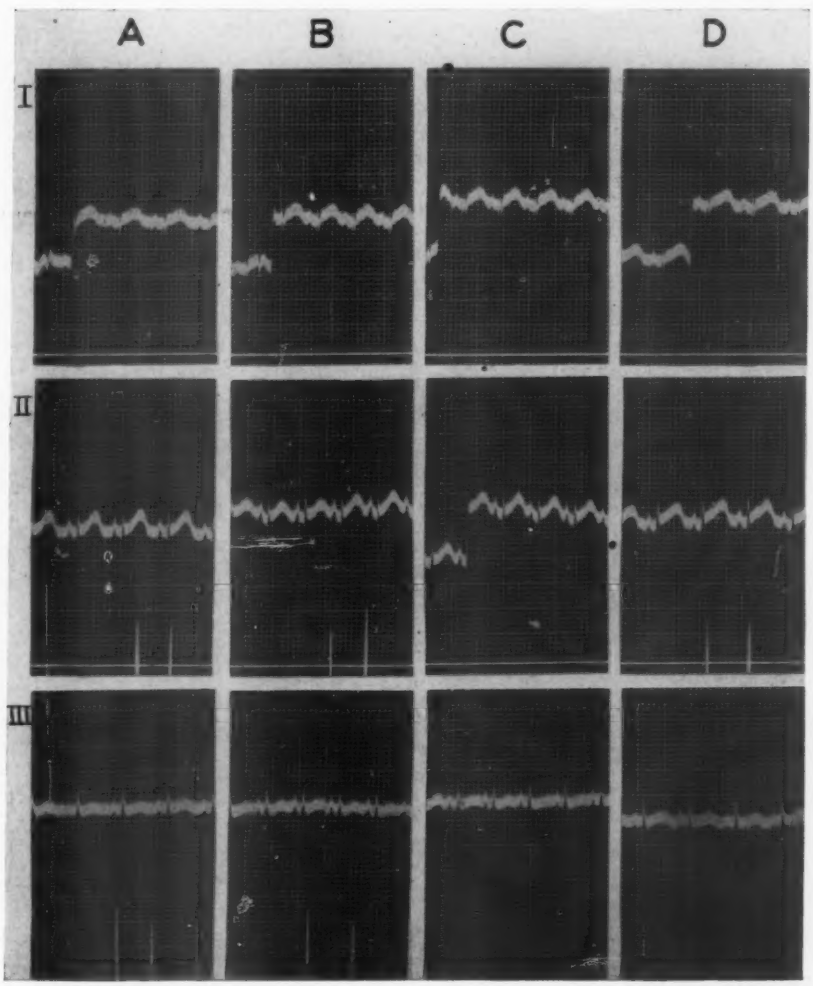

Fig. 1(*c*).—Cat No. 22, electrocardiograms taken twenty days after operation. (Legend as in Fig. 1 (*a*).)

The protocol of a representative experiment is presented below (Cat No. 22). Anoxemia induced by breathing a mixture containing 10 per cent oxygen preoperatively caused no RS-T deviation; changes in T-wave amplitude were negligible. Coronary artery ligation resulted in upward deviation of the RS-T segment in all leads, and anoxemia increased the deviation in two of them. The anoxemia had little effect on the T waves, which, following the operation, had increased in amplitude. There was prompt return to the preanoxemic form after the restoration of air. One week later the RS-T deviations had increased in one lead, and had started to regress in the other two. Anoxemia exaggerated the deviation in two leads, and changed the direction of deviation in the other. Repetition of the procedure after twelve

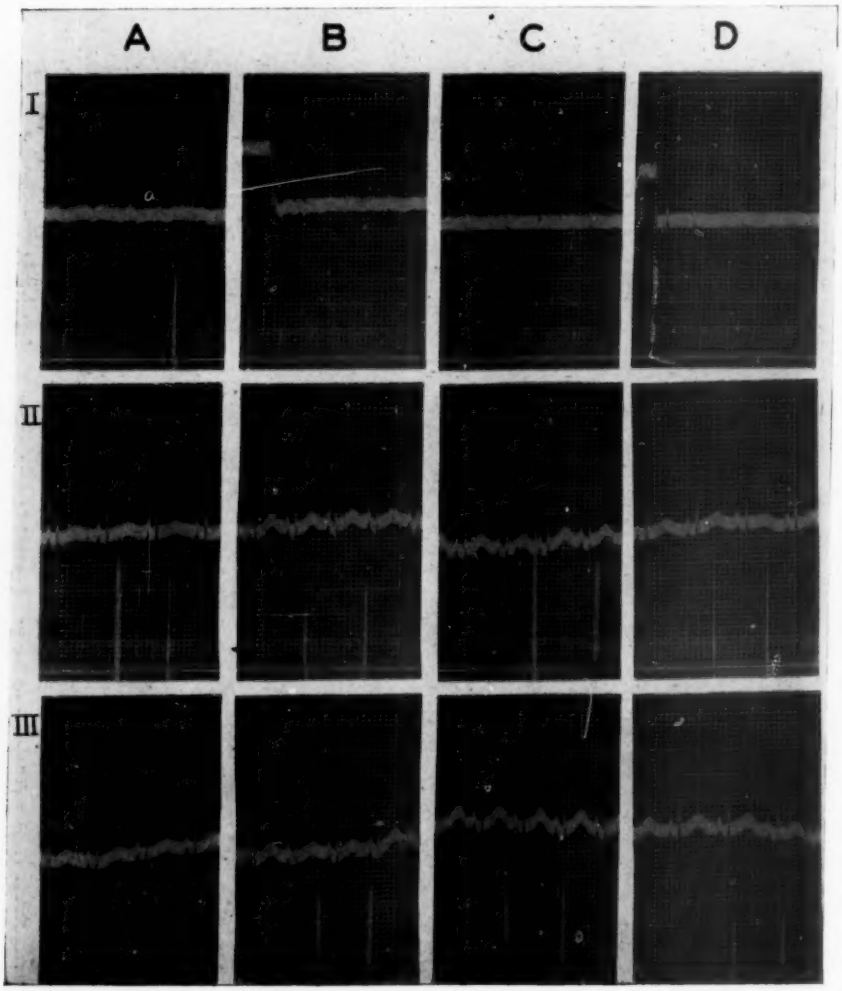

Fig. 1(*d*).—Cat No. 22, electrocardiograms taken forty-seven days after operation. (Legend as in Fig. 1(*a*).)

and twenty-two days, respectively, reproduced the changes which were present on the seventh day. The electrocardiogram, meanwhile, had begun to approach normal. By the twenty-ninth and forty-seventh days after ligation, the RS-T segments had become isoelectric. Again, the induction of anoxemia was followed by an approximation of the changes which occurred directly after ligation. Figs. 1 and 2 show the electrocardiographic progress of cats No. 22 and 28, with the effects of induced anoxemia before and after operation, and during the postoperative course. Fig. 3 suggests a parallelism between the size of the infarct and the electrocardiographic changes induced by anoxemia; the cats with the larger infarcts showed the more extensive electrocardiographic changes.

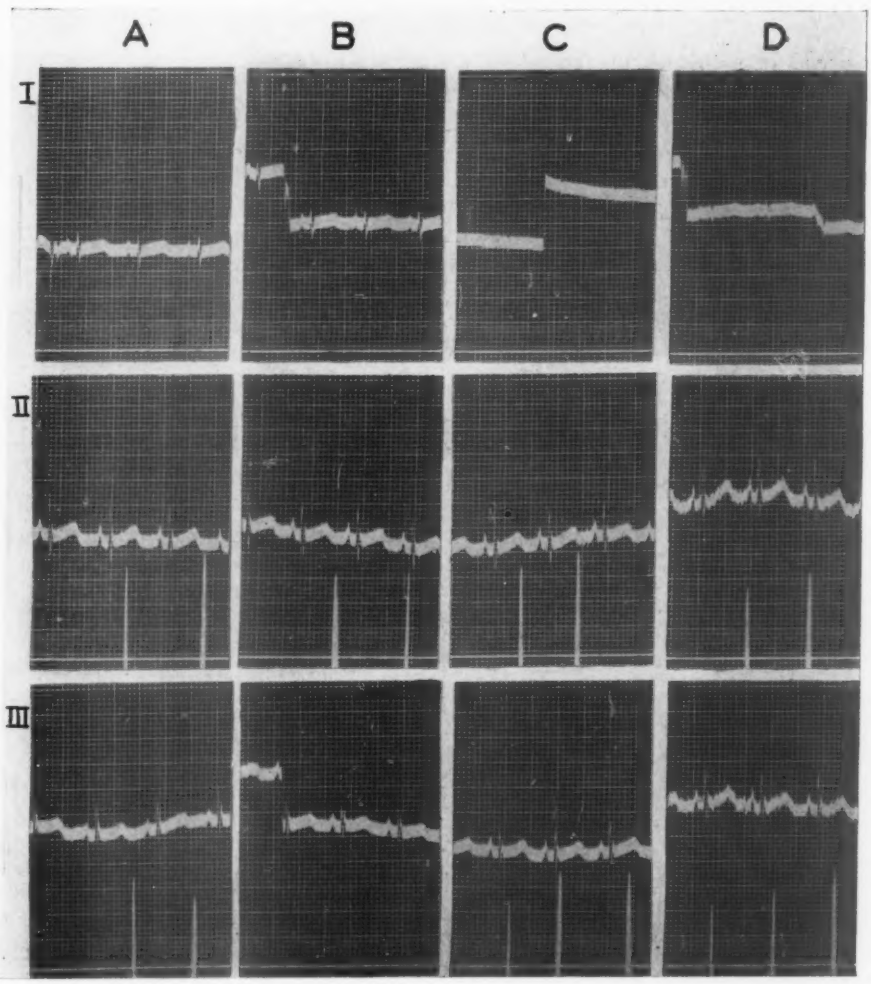

Fig. 2(*a*).—Cat No. 28, preoperative control electrocardiograms. (Legend as in Fig. 1(*a*).)

DISCUSSION

The data analyzed in the preceding section indicate that only the deviations of the RS-T segment which result from ligation or from ligation and anoxemia were consistently indicative of myocardial damage. Other electrocardiographic changes did occur after coronary ligation and during induced anoxemia, but they were both inconstant and inconsistent, and could not be used as reliable criteria of coronary insufficiency. The administration of a mixture containing 10 per cent oxygen to the cats before coronary ligation resulted in no RS-T changes, although the T wave was occasionally affected. T-wave inversion was induced consistently by the greater degree of anoxemia resulting from the administration of an atmosphere containing 5 per

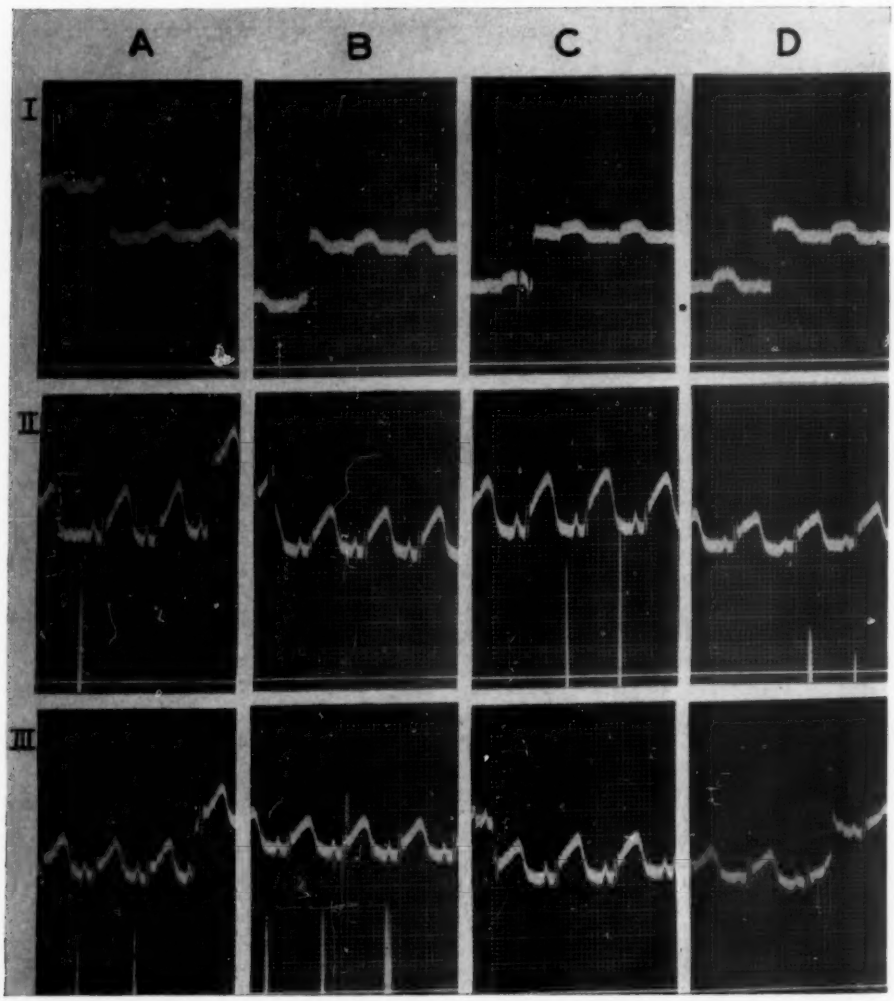

Fig. 2(*b*).—Cat No. 28, electrocardiograms taken immediately after operation. (Legend as in Fig. 1(*a*).)

cent oxygen. These observations are in general agreement with those of other investigators.[14, 18] Deviations in the RS-T segments in dogs resulted from an arterial oxygen saturation lower than 50 per cent in one series,[18] and from a partial pressure of 56 mm. of mercury in another.[15]

The RS-T changes which appear following coronary occlusion and during attacks of angina pectoris have been generally ascribed to ischemia, with resulting anoxia of the involved myocardium. The RS-T changes which have been produced by asphyxia and by marked anoxemia, as well, were not evoked in this series of cats by the degree of anoxemia induced by having them breathe a mixture containing 10 per cent oxygen. After coronary ligation, this degree of anoxemia

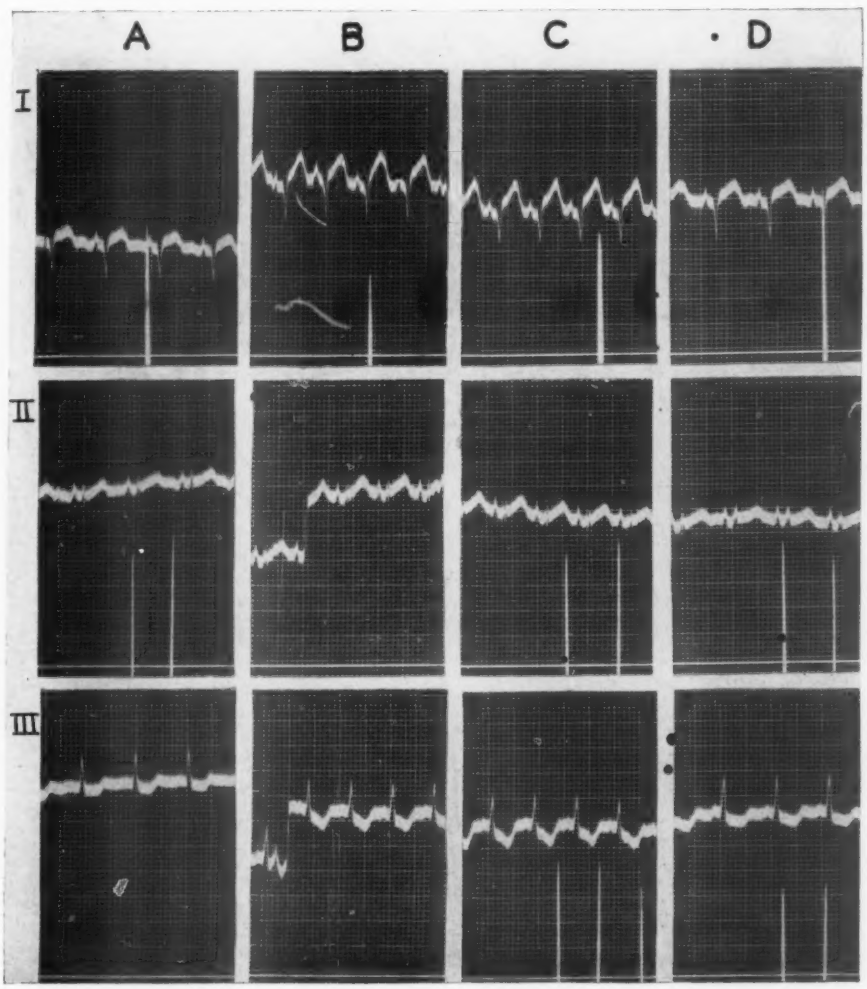

Fig. 2(*c*).—Cat No. 28, electrocardiograms taken thirty-five days after operation. (Legend as in Fig. 1(*a*).)

increased the RS-T deviations in twelve of fourteen cats. It reproduced these changes in nine of the ten cats (Table II) in which the RS-T deviations following coronary ligation had disappeared.

Brief mention of the pathology of cardiac infarction may clarify the theoretical basis for the electrocardiographic changes observed. An experimental cardiac infarct is composed of a central area of extreme ischemia, surrounded by a relatively narrow periphery of edematous, anemic, but still viable, myocardium. In this outer area and from the adjacent myocardium, vascular anastomoses of greater or lesser degree occur. Since the electrocardiogram frequently resumes normal contours when a fibrotic area is present, it is suggested that the electrocardiographic changes are caused by the local myo-

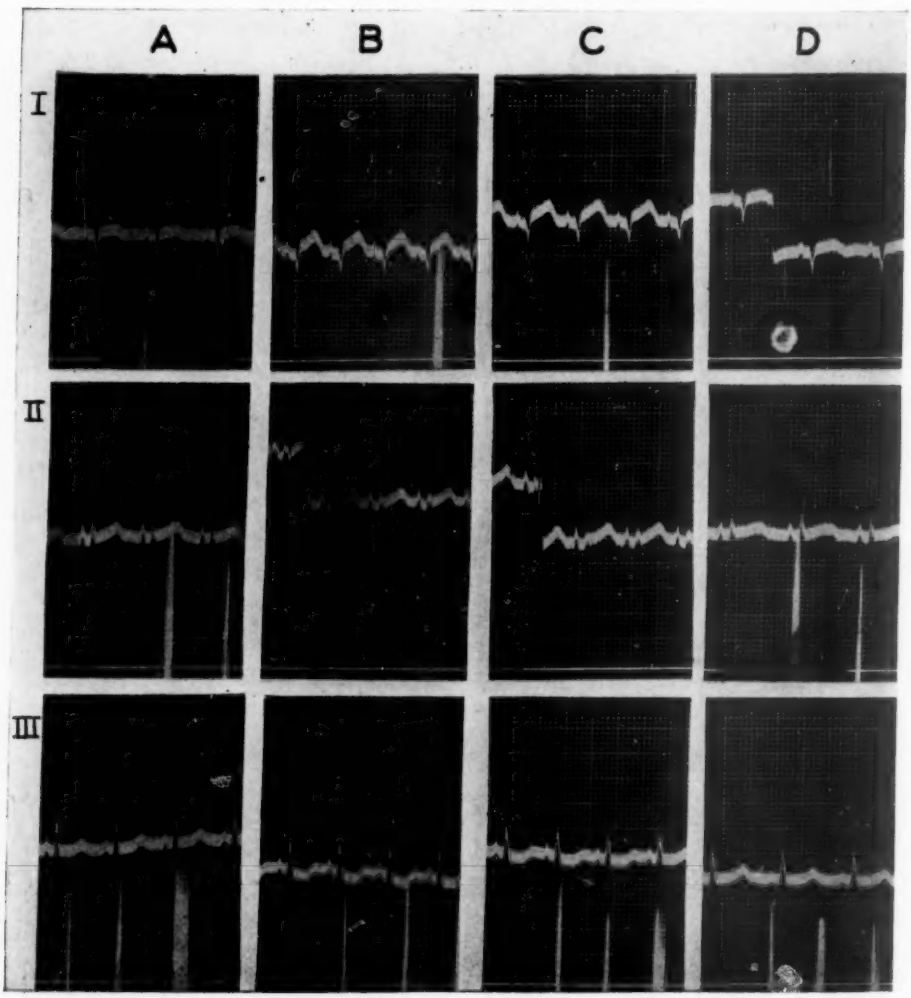

Fig. 2(*d*).—Cat No. 28, electrocardiograms taken fifty days after operation. (Legend as in Fig. 1(*a*).)

cardial anoxia, and not merely by an area of scar tissue. The area at the periphery of the infarct is usually in a constant state of relative anoxia. With healing there are fibrosis of the infarct, improved local vascularity, and regression of the electrocardiographic changes. If it is assumed that these electrocardiographic changes were the result of local myocardial anoxia, it should be possible to cause their reappearance by the induction of mild anoxemia, thereby raising the level of local anoxia above the threshold for their manifestation. This was actually accomplished. In the instances in which anoxemia failed to induce electrocardiographic changes in the experimental cats it may be that there was a sharper demarcation of infarct from healthy muscle, with an area of relative ischemia too small to result in a supraliminal degree of anoxia, but an increase in the degree of induced anoxemia by the use of a mixture containing 5 per cent oxygen resulted in electrocardiographic changes in one of two cats.

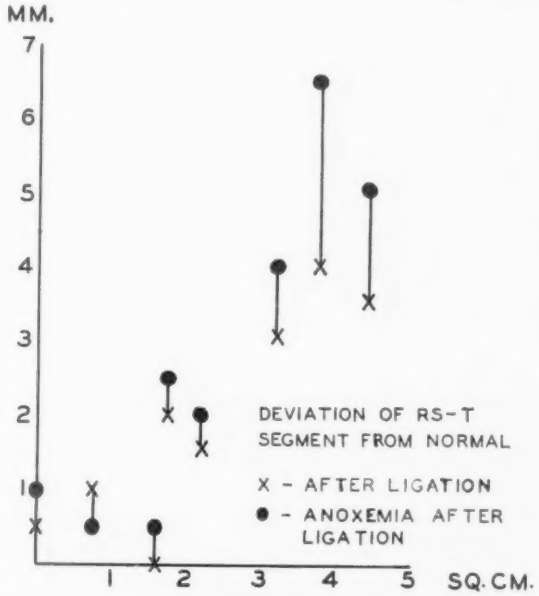

Fig. 3.—Abscissa, area of infarct. Ordinate, deviation of RS-T segment.

Coronary ligation impairs the blood flow only to that portion of the myocardium supplied by the ligated vessel. On the other hand, patients with coronary arteriosclerosis, to whom this test might be applied, have more widespread impairment of cardiac blood supply without, necessarily, a true, major infarction. Therefore, in such patients the induction of mild anoxemia may be expected to increase the local myocardial anoxia sufficiently to produce characteristic electrocardiographic changes in a manner similar to that suggested by this study. The results of this work, when considered in conjunc-

tion with those of Levy, et al.,[1] on patients suspected of having coronary disease, justify the use of this test in the differential diagnosis of coronary insufficiency.

SUMMARY

1. Under sodium pentobarbital anesthesia, anoxemia was induced by the administration of an atmosphere containing 10 per cent oxygen in fourteen cats before, and at intervals after, ligation of the left branch of the left anterior descending coronary artery.

2. The RS-T segment of the electrocardiogram, which was unaffected by preoperative induction of anoxemia, was made to increase in deviation by postoperative induction of anoxemia in twelve of fourteen cats.

3. The RS-T segment returned to an isoelectric position in ten cats, despite the persistence of the infarct, as shown at autopsy. The deviation originally produced by coronary ligation was reproduced by anoxemia in nine of these cats.

4. Control observations disclosed that the changes observed were not caused by anesthesia, change in blood pressure, or pericardiotomy alone.

5. The physiologic basis for the changes observed is discussed. It may be concluded from these observations that the effect of induced anoxemia is a rational test for coronary insufficiency.

REFERENCES

1. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. Med. Sci. **197**: 241, 1939.
2. Leslie, A., Scott, W. S., Jr., and Mulinos, M. G.: Effect of Anoxemia Upon Electrocardiogram of Cats After Coronary Ligation, Proc. Soc. Exper. Biol. & Med. **41**: 652, 1939.
3. Smith, F. M.: Ligation of Coronary Arteries With Electrocardiographic Study, Arch. Int. Med. **22**: 8, 1918.
4. Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W.: Electrocardiographic Changes in Myocardial Ischemia, Am. Heart J. **6**: 522, 1931.
5. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects, Am. Heart J. **9**: 771, 1934.
6. Katz, L. N., and Hamburger, W. W.: Effect of Anoxemia on the Electrocardiogram of Normal Persons, J. A. M. A. **100**: 141, 1933.
7. Ward, G. E. S., and Wright, S.: Electrocardiographic Study of Heart During and After Nitrous Oxide Anesthesia, Lancet **2**: 1184, 1929.
8. Colvin, L. T.: Electrocardiographic Changes in a Case of Severe Carbon Monoxide Poisoning, Am. Heart J. **3**: 484, 1928.
9. Haggard, H. W.: Carbon Monoxide Asphyxia, Am. J. Physiol. **56**: 390, 1921.
10. Rothschild, M. A., and Kissin, M.: Production of Anginal Syndrome by Induced General Anoxemia, Am. Heart J. **8**: 729, 1933.
11. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing ST Deviation in the Electrocardiogram, Am. Heart J. **8**: 745, 1933.
12. Bergman, G. V.: Erstickung im Herzmuskel als Ursach der Angina Pectoris, Deutsche med. Wchnschr. **60**: 1378, 1934.
13. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effect of Induced Oxygen Want in Patients With Cardiac Pain, Am. Heart J. **15**: 187, 1938.

14. Binet, L., Strumza, M. V., and Ordonez, J. H.: Modifications de l'Electrocardiogramme au Cours de l'Anoxhemie Aigue Chez le Chien, Compt. rend. Soc. de biol. **125**: 318, 1937.
15. Binet, L., Strumza, M. V., and Ordonez, J. H.: Coeur et Anoxie, Arch. d. Mal d. Coeur **31**: 11, 1938.
16. Kountz, W. B., and Hammouda, M.: Effects of Asphyxia and Anoxemia on the Electrocardiogram, AM. HEART J. **8**: 259, 1932.
17. Green, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension, Arch. Int. Med. **27**: 517, 1921.
18. Kountz, W. B., and Gruber, C. M.: Electrocardiographic Changes in Anoxemia, Proc. Soc. Exper. Biol. & Med. **27**: 170, 1929.
19. Lewis, T., and Mathison, G. C.: Auriculo-Ventricular Heart Block as a Result of Asphyxia, Heart **2**: 47, 1910.
20. Mathison, G. C.: Cause of Heart Block Occurring During Asphyxia, Heart **2**: 54, 1910.
21. Gold, H., Travell, J., and Modell, W.: Effect of Aminophyllin on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, AM. HEART J. **14**: 284, 1937.
22. Hafkesbring, R., and MacCalmont, W.: Effect of Barbital Derivatives on the Electrocardiogram, Am. J. Physiol. **119**: 322, 1937.
23. Kohn, R., and Lederer, L.: Pentothal Studies With Special Reference to the Electrocardiogram, J. Lab. and Clin. Med. **23**: 717, 1938.
24. Volpitto, P. P., and Marangoni, B. A.: Electrocardiographic Studies During Anesthesia With Intravenous Barbiturates, J. Lab. and Clin. Med. **23**: 575, 1938.
25. Lieb, C. C., and Mulinos, M. G.: Some Further Observations on Sodium Iso-Amyl-Ethyl-Barbiturate as a Laboratory Anesthetic, Proc. Soc. Exper. Biol. & Med. **26**: 709, 1929.
26. Gross, L., and Calef, B.: Electrocardiographic Changes in the Dog Following Sudden Occlusion of Left Anterior Descending Coronary Branch, AM. HEART J. **14**: 677, 1937.
27. Harris, B. R., and Hussey, R.: Electrocardiographic Changes Following Coronary Ligation in Dogs, AM. HEART J. **12**: 724, 1936.
28. Barres, A. R., and Mann, F. C.: Electrocardiographic Changes After Ligation of Coronary Arteries of Dog, AM. HEART J. **7**: 477, 1932.
29. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Means of Vacuum Extraction and Manometric Measurement. I. J. Biol. Chem. **61**: 523, 1924.

THE BASAL METABOLIC RATE IN ORGANIC HEART DISEASE

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ALTHOUGH attempts have been made to correlate basal metabolic rate with many physiologic functions, there is very little in the literature relating to basal metabolic rate and cardiovascular phenomena in cardiac disease. From Du Bois'[1] review of the literature up to 1936, it appeared that the basal metabolic rate in severely ill cardiac patients with dyspnea was increased as much as 28 to 49 per cent. If dyspnea was not present, the basal metabolic rate was not increased. Hamburger and Lev[2] were of the opinion that the increase in basal metabolic rate was proportional to the degree of decompensation, since it appeared that all except one of their seventeen patients who had an increase in basal metabolic rate were moderately to severely decompensated. Peabody, Wentworth, and Barker,[3] on the basis of measurements of vital capacity, divided their cases into two groups; in the first group were those patients in whom the vital capacity was more than 60 per cent of normal, and in the second, those in whom it was less than 60 per cent of normal. Those in the first group were all comfortable at rest; their average basal metabolic rate was +2.5 per cent; on the other hand, those in the second group suffered from severe cardiac disease and some were dyspneic at rest; their average basal metabolic rate was +12.8 per cent. In a study of 217 cardiac patients, Boothby and Willius[4] found that the basal metabolic rate was only slightly above normal, regardless of the etiology of the cardiac disease. Dieuaide[5] found that the basal metabolic rate was raised 16.7 per cent in a patient during an attack of ventricular paroxysmal tachycardia. Reznitskaya and Spivak,[6] in a study of 620 cases, found no relation between maximal blood pressure and basal metabolic rate in hypertensive cardiac disease. Nylin[7] found that the basal metabolic rate was increased in patients suffering from cardiac disease. When a digitalis preparation was given intravenously and these patients improved, he observed a transient increase in basal metabolic rate, which was followed by a decrease in those patients who did not have cirrhosis of the liver.

The conclusions of the above studies are summed up by Du Bois,[1] as follows: "In general, it seems that there is nothing in heart disease of itself that alters the metabolism, but that the increased activity of the muscles of respiration causes an increased oxygen consumption."

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Stewart, Deitrick, and Crane,[8] in a study of four cases of spontaneous myxedema, both before and during thyroid therapy, found a linear correlation between oxygen consumption and circulation time, oxygen consumption and arteriovenous oxygen difference, and basal metabolic rate and arteriovenous oxygen difference. In other words, as the oxygen consumption increased and the basal metabolic rate approached normal, there was a decrease in circulation time and a decrease in arteriovenous oxygen difference. In a similar manner, in this investigation an attempt has been made to correlate basal metabolic rate with the functional state of cardiac patients and with arteriovenous oxygen difference, circulation time, venous pressure, cardiac area, and left ventricular work.

METHODS

All observations were made in a similar fashion in the morning, with patients in a basal metabolic state. During the measurements of oxygen consumption the patients sat in a steamer chair (at an angle of 135°), with the legs extended. Oxygen consumption was measured with a Benedict-Roth metabolism apparatus, and the basal metabolic rate was calculated from Mayo Foundation Standards for age and sex,[9] and the surface area tables of Du Bois and Du Bois.[10]

Measurements of arteriovenous oxygen difference[11, 12] were taken from cardiac output data on these patients.

Arm-to-tongue circulation time was estimated by the use of decholin; 5 c.c. of a 20 per cent solution were injected in one or two seconds into an antecubital vein while the patient was lying quietly in the supine position. This was repeated in one and one-half minutes. The time was recorded from the beginning of the injection until the patient perceived the bitter taste.

Measurements of cardiac area were made by the technique of Levy.[13]

The vital capacity was computed as per cent of normal by the method of West, as described by Lemon and Moersch.[14]

Three hundred sixty basal metabolic estimations were made on 140 patients. The patients fell into the following groups: sixty-five patients suffering from heart disease who had never experienced heart failure; twenty-seven exhibiting signs and symptoms of heart failure at the time of the observations; twenty-two who had recovered from congestive heart failure; twelve who were followed from failure to compensation; fourteen on whom estimations were made during the presence of cardiac irregularities and again after return to normal sinus rhythm; and, finally, the pericardial group, which included eight patients suffering from chronic constrictive pericarditis, three recovering from pericarditis with effusion, and three exhibiting pericardial effusion.

Basal Metabolic Rate and Physiologic State of Cardiac Patients.—The average* of 110 basal metabolic rate estimations on sixty-five cardiac patients who had never experienced heart failure was –1 per cent. The average of sixty-three basal metabolic rate estimations on twenty-seven patients during failure was +7 per cent, and of forty-one on twenty-two patients after they had recovered from failure was also –1 per cent (Fig. 1*A*). A number of these patients had auricular fibrillation. The

*The averages were obtained by adding the basal metabolic rates and dividing by the number of estimations.

average for the normal rhythm group alone, before failure, was –2 per cent, during failure +10 per cent, and after recovery –1 per cent (Fig. 1*B*). On the other hand, the average for the auricular fibrillation group before failure was +2.5 per cent, only +3 per cent during failure, and –1 per cent for the group which had recovered from failure (Fig. 1*C*).

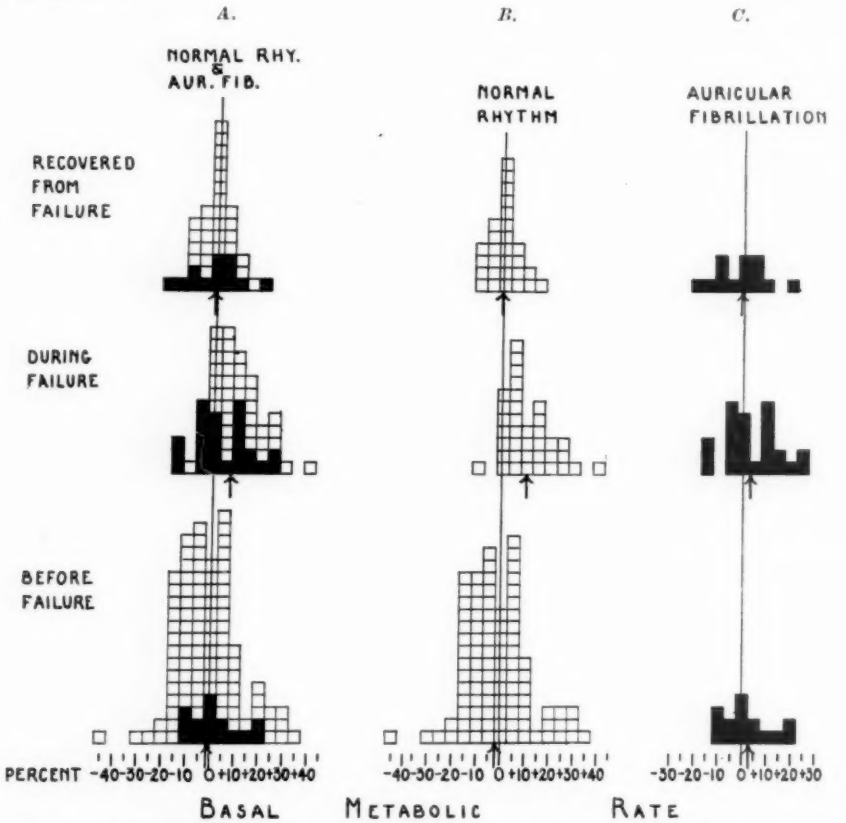

Fig. 1.—Basal metabolic rate and functional state of cardiac patients. In *A* are plotted as frequency diagrams the data relating to the basal metabolic rates of patients grouped on a functional basis, namely, those who had never suffered heart failure, those with failure, and those who had recovered from failure, and those with normal rhythm as well as those with auricular fibrillation. In *B* and *C* the data on the two rhythms are separated. In this figure, as well as in Fig. 2, each block represents one basal metabolic rate estimation, and arrows indicate the average for the group.

Basal Metabolic Rate and Cardiac Arrhythmia.—There were forty-five basal metabolic rate estimations on fourteen patients who had certain paroxysmal irregularities, namely, auricular fibrillation, auricular flutter, and supraventricular and ventricular tachycardia. Twenty-one of these were carried out when the irregularity was present; their average basal metabolic rate was +7 per cent. The average of twenty-four estimations in this same group after return to normal sinus rhythm was +1 per cent (Fig. 2*A*).

Basal Metabolic Rate and Dyspnea.—The patients who suffered from heart failure were divided into those who had dyspnea and those who did not. The average of twenty-nine basal metabolic rate estimations on eighteen patients with heart failure and dyspnea was +10 per cent. On the other hand, the average of thirty-four basal metabolic rate estimations on nine patients with heart failure who did not have dyspnea was +5 per cent (Fig. 2*B*).

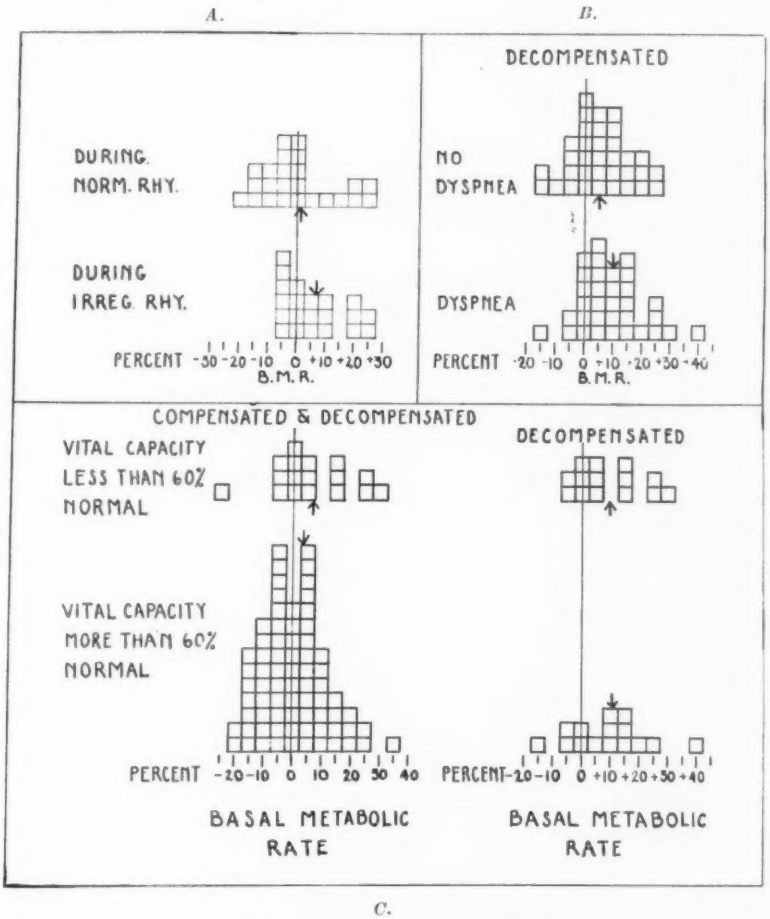

Fig. 2.—In *A* are recorded as frequency diagrams the data relating to the basal metabolic rates during paroxysmal cardiac irregularities and after restoration of normal rhythm. In *B* are plotted as frequency diagrams the basal metabolic rates of decompensated patients, grouped with respect to presence of dyspnea. In *C* are plotted as frequency diagrams data relating to basal metabolic rate and vital capacity.

Basal Metabolic Rate and Vital Capacity.—In seventy-three cases in which the vital capacity was 60 per cent, or more, of the calculated normal, the average basal metabolic rate was +3 per cent, and, in seventeen cases in which the vital capacity was less than 60 per cent of normal, the average basal metabolic rate was only +6 per cent (Fig. 2*C*); this is in contrast to Peabody's[3] averages of +2.5 per cent and +12 8 per cent,

respectively. On the other hand, of twenty-nine patients who were suffering from heart failure, fifteen had vital capacities of more than 60 per cent, and fourteen of less than 60 per cent, of normal. The average basal metabolic rate in the two groups was +10.4 per cent and +9.4 per cent, respectively (Fig. 2*C*). It does not appear from this analysis that vital capacity is an accurate index of the degree of decompensation, or that there is a significant relation between the level of decreased vital capacity and that of increased basal metabolic rate.

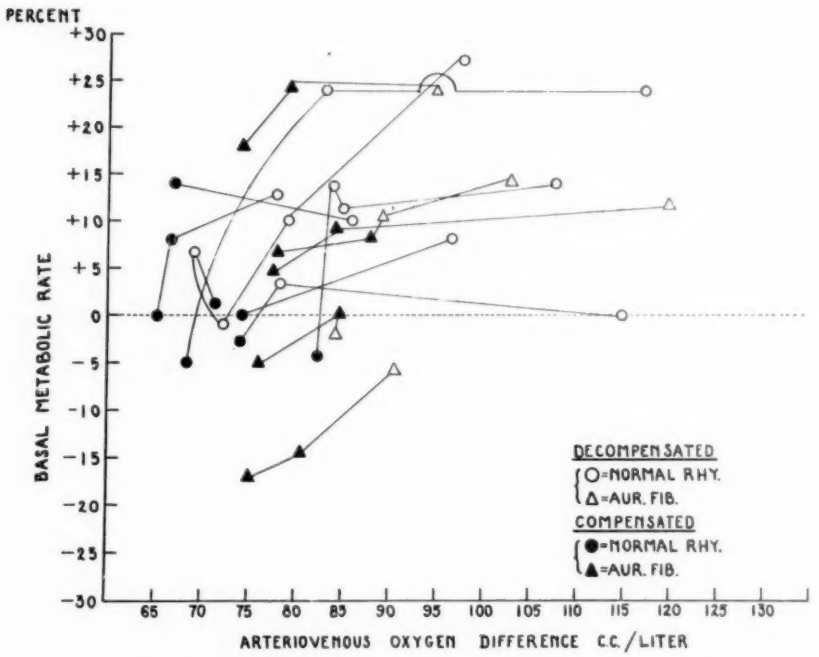

Fig. 3.—In this figure the basal metabolic rate is plotted against arteriovenous oxygen difference in patients followed from the stage of decompensation to restoration of compensation. During failure the basal metabolic rates are higher, and the arteriovenous oxygen difference greater, than after restoration of compensation.

Basal Metabolic Rate and Other Measurements of the Circulation.—In the group of patients who had never experienced heart failure, there appeared to be no correlation between basal metabolic rate and arteriovenous oxygen difference, or circulation time, or venous pressure, or heart size, or left ventricular work. During heart failure the average basal metabolic rate increased slightly, as did the average arteriovenous oxygen difference, circulation time, venous pressure, and heart size, while the left ventricular work decreased, but there was no linear correlation between any of these measurements and the basal metabolic rate. After recovery from failure the basal metabolic rate, circulation time, venous pressure, and heart size decreased, and left ventricular work increased.

A few patients were observed while they had failure and after they recovered. Although, on plotting the data, no two of the cases followed the same line, the group suffering from failure exhibited an increased basal metabolic rate, as well as an increased arteriovenous oxygen difference (Fig. 3), venous pressure, circulation time, and heart size, and decrease in left ventricular work, which was succeeded by a decrease in metabolism, a decrease in arteriovenous oxygen difference, in circulation time, in venous pressure, and in heart size, and an increase in left ventricular work, as compensation returned. In a similar fashion, in seven cases of chronic constrictive pericarditis no linear correlation between basal metabolic rate and measurements of the circulation was apparent.

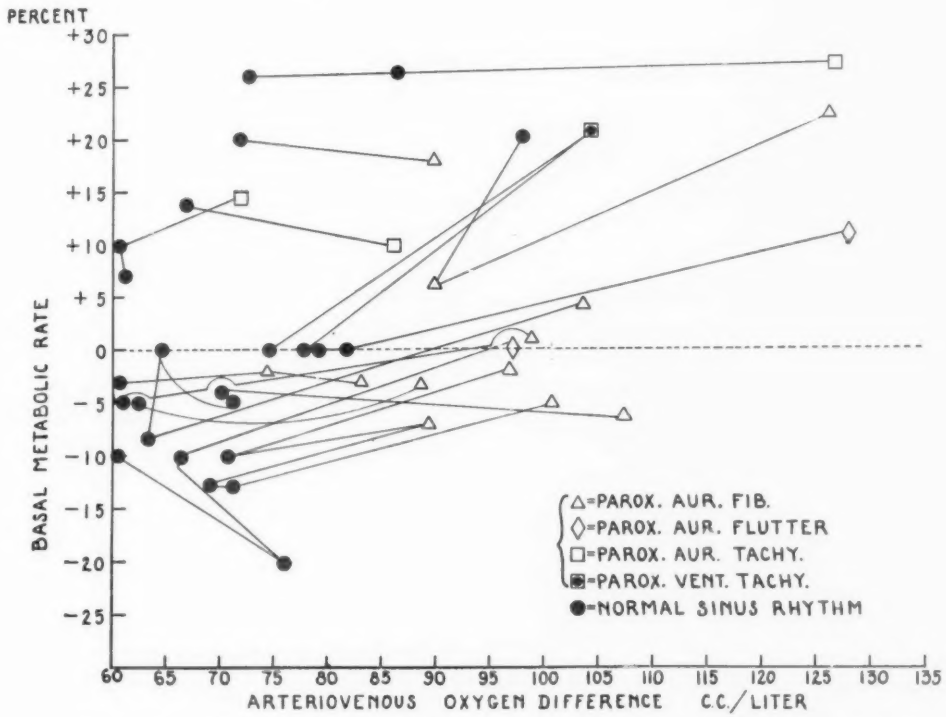

Fig. 4.—In this figure basal metabolic rate is plotted against arteriovenous oxygen difference for the paroxysmal tachycardia group. As normal sinus rhythm replaces the irregularity the trend is toward a lower basal metabolic rate, with a smaller arteriovenous oxygen difference.

The patients with arrhythmias who were followed from the time when the irregularity was present until normal rhythm was restored showed, for the most part, the same changes as the patients who were followed from failure to compensation. The increase in basal metabolic rate during the irregularity was definite, though not marked, and there were an increase in arteriovenous oxygen difference (Fig. 4), circulation time, venous pressure, and in heart size, and a decrease in left

ventricular work. With return to normal rhythm there were a decrease in basal metabolic rate, in arteriovenous oxygen difference, in circulation time, in venous pressure, and in heart size, and an increase in left ventricular work. The changes do not appear to depend upon the type of the irregularity.

No correlation between systolic blood pressure and basal metabolism could be established, either in cases of hypertensive heart disease or in other types of heart disease in which the blood pressure was at a normal level.

DISCUSSION

An attempt has been made to correlate basal metabolic rate, the functional state, and several measurements of the circulation in a group of patients suffering from organic cardiac disease. Patients were classified on a functional rather than an etiologic basis. The lack of close correlation was apparent, and was in large measure a result of the wide variations in basal metabolic rate, even in patients who had never experienced failure. Even though separating out and dealing only with the cases of rheumatic heart disease eliminated many of the extremes of basal metabolic rate, a closer correlation did not appear.

There was a slight, but definite, increase in the average basal metabolic rate during heart failure, with a return toward normal after recovery from failure. Some of these patients exhibited quite marked changes, but the averages for the groups did not reveal as much variation as other investigators have found. The magnitude of increase in basal metabolic rate did not parallel the degree of decompensation, an observation which differs from the opinion expressed by Hamburger and Lev.[2]

When the analysis is made with respect to dyspnea, it appears that the presence of this symptom is a significant factor in raising the basal metabolic rate during heart failure. This is in agreement with the observations of others.[1] The increase in basal metabolic rate, however, does not appear to be entirely the result of the increased muscular effort of dyspnea. Evidence for this view is at hand in the observation that the group of patients without dyspnea but with other signs of decompensation exhibited an increase in average basal metabolic rate, although it was not so great (Fig. 2 *A* and *B*). All of these observations were made on patients who were able to breathe satisfactorily during the rebreathing carried out for the estimation of the arteriovenous oxygen difference as a part of the measurement of cardiac output; these averages might have been higher had more extremely dyspneic patients been studied.

Likewise, when the relationship between vital capacity and basal metabolic rate was investigated, we found that the basal metabolic rate increased in patients whose vital capacity was diminished (Fig.

2C), but not to so great an extent as that observed by Peabody, Wentworth, and Barker.[3] There did not appear to be a significant correlation between the level of decrease in vital capacity and the level of increase in basal metabolic rate.

The patients who had auricular fibrillation were separated from those whose cardiac mechanism was normal. Before failure, the basal metabolic rates in both groups showed the same variations; approximately as many were above normal as below (Fig. 5). This was the case also in the groups in which the basal metabolic rate estimations were made after recovery from failure. During failure, however, the variations of basal metabolic rate in patients who had auricular

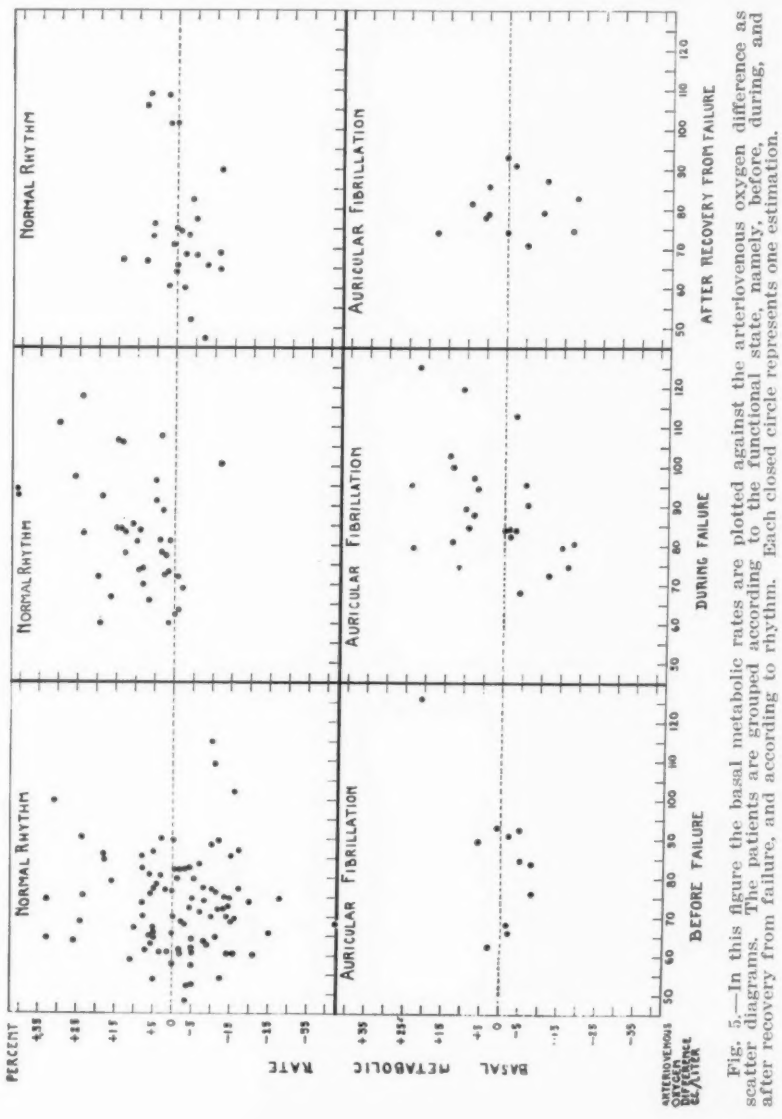

Fig. 5.—In this figure the basal metabolic rates are plotted against the arteriovenous oxygen difference as scatter diagrams. The patients are grouped according to the functional state, namely, before, during, and after recovery from failure, and according to rhythm. Each closed circle represents one estimation.

fibrillation did not change; the rates were scattered both above and below zero. In those patients with normal rhythm, however, there was not only a definite rise in average metabolism, but in all except five patients the metabolism was above zero (Fig. 5). That this was not because there was a smaller number of patients who had auricular fibrillation is apparent from this scatter diagram. It appears that the presence of auricular fibrillation in some manner prevented an increase in basal metabolism when failure took place.

In those patients whom it was possible to follow from heart failure to recovery or from an irregularity to normal rhythm, it was found that with restoration to compensation or return to normal sinus rhythm the basal metabolic rate fell, the arteriovenous oxygen difference decreased, circulation time became shorter, venous pressure fell, cardiac size decreased, and the left ventricular work per beat increased. Although no two patients followed the same linear pattern, the trend in most cases was in the same direction; in short, all of these functions, namely, basal metabolic rate, arteriovenous oxygen difference, circulation time, venous pressure, cardiac size, and left ventricular work, appear to be dependent upon some other factor.

When patients who had never had failure were fully digitalized, no apparent effect on the metabolism was observed, which is in contrast to the changes which have been described in the presence of failure.

Finally, since Cohn and Steele have called attention to the occurrence of fever in heart failure,[15, 16, 17] we tried to ascertain whether there was a correlation between basal metabolic rate and the presence of fever. For this purpose we analyzed the temperature curves of the patients whose data are plotted in Fig. 5. A rise in temperature occurred only five times on the day of the metabolic test, as compared with 211 tests when there was no fever. In those five the range of the basal metabolic rate was from –4 per cent to +22 per cent, whereas the range in those without fever was from –45 per cent to +41 per cent. Obviously, an increase in basal metabolic rate is not to be accounted for by the presence of fever.

We were unable in this series to correlate basal metabolic rate with cardiac output, as Starr, et al.,[18, 19] have done, because, with the Grollman technique for measuring cardiac output, the oxygen consumption is used in the calculations.

CONCLUSIONS

1. The basal metabolic rate was increased, on the average, by 8 per cent during cardiac decompensation of the severity which we studied. The high range in patients who did not have failure was as great, but in this group there were more rates below zero.

2. Decreased vital capacity and dyspnea were apparently not the only factors which were operative in the production of increased oxygen consumption, although they may have been the most important.

3. No increase in basal metabolic rate could be attributed to the presence of fever.

4. No correlation could be detected between basal metabolic rate and arteriovenous oxygen difference, circulation time, venous pressure, heart size, and left ventricular work, unless individual patients were followed through from failure to compensation. In these latter cases, as compensation took place a decrease in oxygen consumption was accompanied by a decrease in arteriovenous oxygen difference, in circulation time, in venous pressure, and in cardiac area, and by an increase in left ventricular work. In short, the increased basal metabolic rate and these other functions appear to be dependent on the same factor.

5. When normal sinus rhythm replaced certain cardiac irregularities, the changes were similar to those which were observed when compensation succeeded failure, with the exception that there was no correlation between basal metabolic rate and venous pressure.

6. In patients with auricular fibrillation the basal metabolic rate varied markedly, and as many were above zero as below when the patients had failure. On the other hand, if normal rhythm prevailed, nearly all of the basal metabolic estimations were above zero when failure occurred.

7. Digitalis, in the manner in which we gave it, had no effect on basal metabolic rate except in so far as it helped to abolish congestive failure.

REFERENCES

1. Du Bois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Ed. 3, 1936, p. 398, Lea and Febiger.
2. Hamburger, W. W., and Lev, M. W.: Basal Metabolism in Organic Heart Disease With Decompensation, J. A. M. A. **84**: 587, 1925.
3. Peabody, F. W., Wentworth, J. A., and Barker, B. L.: Clinical Studies on the Respiration. V. Basal Metabolism and the Minute Volume of the Respiration of Patients With Cardiac Disease, Arch. Int. Med. **20**: 468, 1917.
4. Boothby, W. M., and Willius, F. A.: The Basal Metabolic Rate in Cases of Primary Cardiac Disease, Med. Clin. N. A. **8**: 1171, 1925.
5. Dieuaide, F. R.: Observations on the Respiratory Gases in Ventricular Paroxysmal Tachycardia, Bull. Johns Hopkins Hosp. **35**: 229, 1924.
6. Reznitskaya, E. Y., and Spivak, R. Y.: Basal Metabolism in Hypertonia, Klin. med. **16**: 1410, 1938.
7. Nylin, G.: Effect of Large Doses of Digitalis on Standard Metabolism, J. Lab. and Clin. Med. **23**: 472, 1938.
8. Stewart, H. J., Deitrick, J. E., and Crane, N. F.: Studies of the Circulation in Patients Suffering From Spontaneous Myxedema, J. Clin. Invest. **17**: 237, 1938.
9. Boothby, W. M., Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism, With a Nomogram for Clinical Application, Am. J. Physiol. **116**: 468, 1936.
10. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**: 863, 1916.
11. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., 1932, p. 73, C. C. Thomas Co.

12. Grollman, A., Friedman, B., Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining Cardiac Output in Patients With Cardiac Disease, J. Clin. Invest. **12**: 751, 1933.
13. Levy, R. L.: The Size of the Heart in Pneumonia. A Teleroentgenographic Study, With Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**: 359, 1923.
14. Lemon, W. S., and Moersch, H. J.: Comparison of Constants for the Determination of Vital Capacity, Arch. Int. Med. **33**: 118, 1924.
15. Cohn, A. E., and Steele, J. M.: Unexplained Fever in Heart Failure, J. Clin. Invest. **13**: 853, 1934.
16. Steele, J. M.: Fever in Heart Failure. Relations Between the Temperatures of the Interior and the Surface of the Body, J. Clin. Invest. **13**. 869, 1934.
17. Steele, J. M.: Fever in Heart Disease, Internat. Clin. 1, Series **46**: 17, 1936.
18. Starr, I. Jr., Collins, L. H., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Invest. **12**: 13, 1933.
19. Starr, I., Jr., Donal, J. S., Margolies, A., Shaw, R., Collins, L. H., and Gamble, C. J.: Studies of the Heart and Circulation in Disease, Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in 235 Subjects, J. Clin. Invest. **13**: 561, 1934.

Department of Clinical Reports

PERICARDIAL EFFUSION IN MYXEDEMA

Report of a Case in Which the Intrapericardial Pressure Was Measured

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THE literature on the subject of myxedema heart disease began with the original report of Zondek,[1] in which he described it as a clinical entity. Similar reports by Assmann,[2] Meissner,[3] and Fahr[4] followed. Other observers questioned the existence of such an entity. Among these were Willius and Haines[5] and Christian.[6] More recently, the original idea has been supported by Means, White, and Krantz,[7] Holzman,[8] Davis,[9] Tung,[10] and Ayman, et al.[11] Gallagher[12] reports a case and gives the criteria for diagnosis. In general, the manifestations these writers describe are those of congestive heart failure. With thyroid extract therapy the heart grows smaller, and when the therapy is discontinued it again enlarges, which gives rise to the expression "accordion" or "reversible" heart.

More recently, since the report of Gordon,[13] in 1929, evidence has been found that at least part of the cardiac enlargement in myxedema may be caused by pericardial effusion. Gordon, in his report, described the case of a 68-year-old man who had typical myxedema, with a gross increase in the transverse cardiac diameter. Thyroid extract therapy was effective in remedying both of these conditions. During treatment, large amounts of pericardial fluid were aspirated on several occasions, and once the withdrawal of 1,700 c.c. of fluid reduced the transverse cardiac diameter by 7 cm. Freeman,[14] Evans,[15] and Marzullo and Franco[16] have reported similar cases.

That the condition occurs in lower animals was recognized by Tatum,[17] in 1912, when he found pericardial effusion in thyroidectomized animals. Goldberg,[18] in 1927, performed thyroidectomies on sheep and goats, and, two years later, at autopsy, found that pericardial effusion was present. The hearts of these animals were pale and flabby, and microscopic sections showed disintegration of the heart muscle fibers.

The following case is presented because of its apparent rarity, and because it served to demonstrate how intrapericardial pressure may be measured during the investigation of such cases.

CASE REPORT

Mrs. R. C. (2082-39) was admitted Dec. 2, 1938, under the care of Dr. W. Hurst Brown and was discharged Feb. 2, 1939.

Received for publication Aug. 23, 1939.

History.—This patient was in good health until 1933, when she first noticed weakness and loss of appetite. These symptoms grew gradually worse until, in 1936, her hair became dry and brittle and began to fall out. About at this time her vision became so poor that she could not read street signs. She suffered considerably from distention and eructation of gas after meals. Severe constipation made the use of laxatives obligatory. For two years she had had shortness of breath and palpitation on climbing one flight of stairs. Her menstrual periods became irregular, more frequent (every two or three weeks), more profuse, and were accompanied by a foul-smelling discharge. With each period she noticed small hemorrhages beneath the skin which passed away in a few days. Her skin became dry and scaly, and there were puffy patches under her eyes. Her appearance became so changed that friends would pass her in the street without recognizing her. Her voice became very low, her memory very poor, and her tolerance for cold remarkably reduced. She lost fifteen pounds between 1937 and 1939.

Personal History.—The patient was born in Scotland and had lived in Canada for twelve years. She had been married for eighteen years, and had four healthy children.

Physical Examination.—The patient was a very emaciated white woman, who looked about 70 years old. She had the typical appearance of markedly myxedematous persons, with dry, thin hair and scaling scalp, expressionless face, and pouches of edema beneath deep-set dark-ringed eyes. The vision was poor, but the eye grounds showed only pallor. The mouth was edentulous, and the mucous membranes pale. There were numerous, short, linear, surgical scars in the anterior portion of the neck. The pulse rate was 70; the pulse was regular, rhythmic, and of good volume. The blood pressure was 110/70. On palpation, the apex beat was felt in the fifth left intercostalspace, about 9 cm. from the midline, but the outermost percussion border was 4 cm. to the left of this point, and the heart was enlarged to percussion in all directions. The heart sounds were of fair quality, and no adventitious sounds were heard. The abdomen showed only moderate gaseous distention. The skin over the extremities was thin, atrophic, and scaly, but no myxedematous deposits could be felt except those under the eyes. There was nothing to note about the nervous system except mental changes. Memory and concentration were poor. The patient was mildly depressed, and, at times, suffered great fear of imminent death.

Laboratory Examination.—On admission, the hemoglobin was 68 per cent, the erythrocyte count, 3,200,000, and the leucocyte count, 13,300. The blood smear showed nothing but macrocytosis. The sedimentation rate (uncorrected) was 32 mm. in two hours. The blood Wassermann reaction was negative. The urine contained a very slight trace of albumin; no sugar or acetone was found, and there was nothing unusual microscopically. The two-hour test of renal function showed a maximum variation in specific gravity of 6 points; the ratio of day to night urine volume was 7:4. The nonprotein nitrogen content of the blood was 35 mg. per cent, the serum calcium, 9.9 mg. per cent, and the blood cholesterol, 236 mg. per cent. The glucose tolerance curve was normal.

Four teleoroentgenograms (Figs. 1 to 4) were made during the course of treatment. Fluoroscopic examination showed that the heartbeat produced very little movement of the cardiac borders prior to treatment, and that this movement increased during treatment. Measurements with the orthodiascope were made at frequent intervals. Table I correlates these measurements with the basal metabolic rate, and other observations, during the treatment.

Figs. 5*A* and 5*B* show electrocardiograms which were obtained before treatment, and after six months of treatment, respectively. It will be noted that the voltage was initially low, and that it increased considerably after treatment; the definition of the T waves also improved.

Fig. 1.

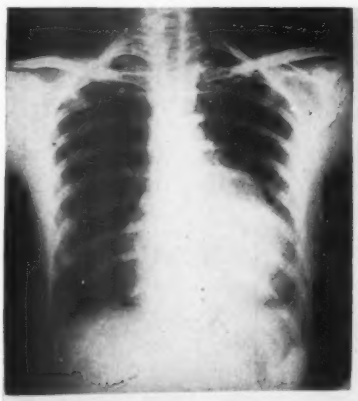


Fig. 2.

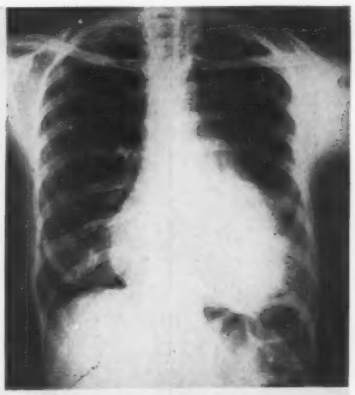


Fig. 3.

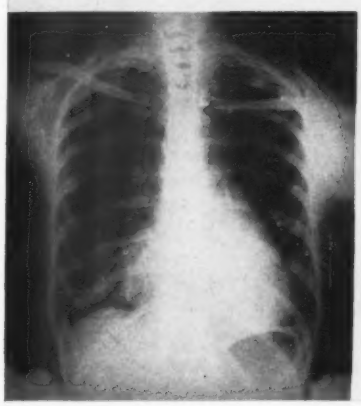
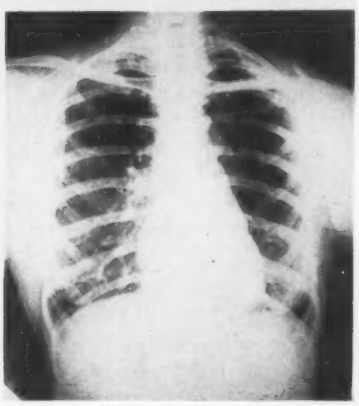


Fig. 4.



Figs. 1 to 4.—These were all made at a distance of 6 feet. Fig. 1 shows the appearance of the heart shadow with the patient in the prone position, and Fig. 2 with her in the vertical position. Both were made Dec. 5, 1938, before she had any treatment. Fig. 3 shows the heart shadow diminishing in size (Jan. 16, 1939), and Fig. 4, taken May 20, 1939, shows the marked diminution in the transverse diameter of the heart after almost six months of treatment.

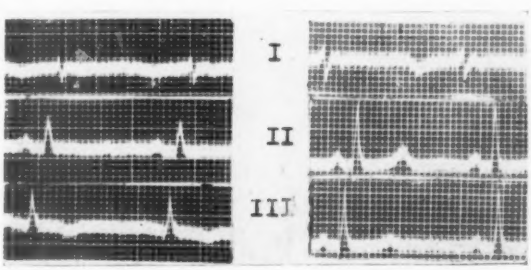


Fig. 5.—These electrocardiograms show the effect of thyroid therapy on the voltage and on the P and T waves. *A* was made Dec. 5, 1938, and *B* was made May 20, 1939, after almost six months of thyroid extract therapy.

TABLE I

TREATMENT AND PROGRESS

DATE	WEIGHT IN LB.	HB.	R.B.C. PER C.MM.	B.M.R.	CARDIO-THORACIC RATIO (CM.)	DAILY* THYROID EXT. DOSE (P.D.)	PULSE RATE
Dec. 3, 1938	89	68%	3.2	-45	15.5/23		72
Dec. 10, 1938						gr. ii	
Dec. 14, 1938						gr. iiss	
Dec. 19, 1938	81½			- 6	15/22.5	gr. iii	72
Dec. 23, 1938				- 7		gr. ii	84
Dec. 31, 1938	84			-10		gr. iiss	
Jan. 4, 1939						gr. i	110†
Jan. 9, 1939					15/22		
Jan. 16, 1939	86	63%	3.9	-12		gr. i	80
Jan. 25, 1939		72%	3.9	-12			
Feb. 1, 1939				100%		gr. i	
Feb. 26, 1939	83			-16		gr. ii	
Mar. 7, 1939						gr. iss	
Mar. 23, 1939	86			plus 10	11.5/22.5	gr. ss	
May 20, 1939	94			- 8		gr. i	
Jan. 20, 1939	97			-10		gr. i	
Aug. 16, 1939	98½	72%	3.7	- 8	11.1/22	gr. i	86

*The dose recorded opposite any date was given until the next date at which a change is recorded.

†The dose was reduced here because of the rapid pulse rate.

Aspiration of the Pericardial Sac.—Since a difference of opinion arose as to whether excess pericardial fluid was contributing to the cardiac enlargement in this case, aspiration of the pericardial sac under local anesthesia was undertaken. On Dec. 4, 1938, a needle, attached to an airtight syringe, was inserted at a point over the bare area of the heart, and 10 c.c. of straw-colored pericardial fluid were withdrawn. The appearance of a drop of blood, and the perception of a grating sensation through the needle which was synchronous with the heartbeat, were the reasons for discontinuing the aspiration.

Two days later, 150 c.c. of dark blood-stained fluid were aspirated from the pericardial sac; the needle was inserted between the xiphisternum and the last left costal cartilage. The fluid withdrawn on this occasion contained 650,000 erythrocytes per c.mm.; the specific gravity was 1.027, and the smear and cultures were negative for any organism.

Measurement of the Intrapericardial Pressure.—During the course of the second aspiration the intrapericardial pressure was measured in the following way. The patient was lying on her back, with the upper part of her body about fifteen degrees above the horizontal. A needle, attached to an airtight syringe, was inserted into the pericardial sac. Fluid was withdrawn and discharged by means of a three-way tap, without allowing any air to enter the pericardial sac. After about 100 c.c. of the pericardial effusion had been removed in this way, a water manometer (such as is commonly used in a pneumothorax apparatus) was connected to the three-way tap. In this way, measurements of the pressure within the pericardial space could be made without interference or modification by atmospheric pressure. It was found that the intrapericardial pressure was variable; readings from −40 to +10 mm. of water were obtained. The variations which occurred could not be clearly correlated with the respirations and the cardiac cycle.

DISCUSSION

The fact that 10 c.c. of fluid could be aspirated initially from a point over the bare area of the heart seems proof enough that an effusion

existed. This may have been slightly increased by the irritation of the few drops of blood which escaped into the pericardial sac at the first aspiration. Nevertheless, it seems certain that at least a part of the increase in the transverse cardiac diameter was caused by pericardial effusion. It is not possible to say, however, that other factors, related to the heart muscle, did not play a part in this enlargement. In fact, judging from the cases reported by others, in which little change could be observed in the transverse cardiac diameter after the aspiration of as much as 700 c.c. of pericardial fluid, it would seem that other factors definitely play some part in producing the increase in the transverse cardiac diameter.

The value of roentgenograms in the diagnosis of small amounts of pericardial effusion must be questioned. As is well known, it is not necessary to have obliteration of the cardiohepatic angle to make the diagnosis (see Figs. 1 to 4). Furthermore, as is seen in Figs. 1 and 2, there was no difference in cardiac contour when the patient changed from the prone to the vertical position. Fluoroscopic observation of the movement of the heart borders is useful, but may be inconclusive. After exhausting the clinical and radiologic signs, it would seem that aspiration provides the only conclusive proof of the presence of small amounts of pericardial fluid.

The measurement of intrapericardial pressure does not seem to have any great clinical significance, as it is probable that only a very rapid increase, causing cardiac tamponade, has any notable effect. However, since it does no harm, it is interesting to attempt it. The conception that the heart is bathed in a thin film of pericardial fluid makes this attempt impossible under normal circumstances. Experimental measurements usually involve the injection of something into the pericardial sac. However, when an effusion exists, an opportunity presents itself to attach a manometer and read the pressure. One might expect that the same pressure would prevail in the pericardial cavity as in the pleural cavities. These three potential spaces are similar, in that all have serous-lined, airtight, fluid-lubricated walls within the thoracic cage. When, in a case of pleural effusion, the pressure is measured, it is usually found to be between −40 and +10 mm. of water. It is not surprising, therefore, to find that under similar circumstances the pressure is the same in the pericardial cavity. The single measurement which was made in this instance showed that the manometer described by Hamilton[19] might be more satisfactory. It is suggested that the intrapericardial pressure should be measured whenever possible, until more is learned about the values and their fluctuations.

SUMMARY

1. The myxedema heart controversy is reviewed briefly.

2. Cases in which pericardial effusion was proved to coexist with myxedema are listed from the literature.

3. A similar case is reported.

4. Measurement of the intrapericardial pressure with a water manometer is described.

The author wishes to express his thanks to Dr. H. K. Detweiler, Physician-in-Chief, and to Dr. W. Hurst Brown, for permission to publish this report, and for their helpful criticism.

REFERENCES

1. Zondek, H.: Das Myxoedemherz, München. med. Wchnschr. **65**: 1180, 1918.
2. Assmann, H.: Das Myxoedemherz, München. med. Wchnschr. **66**: 9, 1919.
3. Meissner, R.: Zur Klinik des Myxoedemherzens, München. med. Wchnschr. **67**: 1316, 1920.
4. Fahr, G.: Myxoedema Heart, J. A. M. A. **84**: 345, 1925.
5. Willius, F. A., and Haines, G. F.: The Status of the Heart in Myxoedema, Am. Heart J. **1**: 67, 1925.
6. Christian, H. A.: The Heart and Its Management in Myxoedema, Rhode Island M. J. **8**: 109, 1925.
7. Means, J. H., White, P. D., and Krantz, C. I.: Observations on the Heart in Myxoedema With Special Reference to Dilatation and Angina Pectoris, Boston M. and S. J. **195**: 455, 1926.
8. Holzman, J. E.: Myxedema Heart With Report of Two Cases, Am. Heart J. **4**: 351, 1929.
9. Davis, J. C.: Myxoedema Heart With Report of a Case, Ann. Int. Med. **4**: 733, 1931.
10. Tung, C. L.: The Status of the Heart in Myxedema, Am. Heart J. **6**: 734, 1931.
11. Ayman, D., Rosenblum, H., and Falcon-Lesses, M.: Myxoedema Heart Without Evidence of Cardiac Insufficiency, J. A. M. A. **98**: 1721, 1939.
12. Gallagher, J. R.: Myxoedema Heart Disese, With Report of One Case, Yale J. Biol. and Med. **5**: 75, 1932.
13. Gordon, A. H.: Some Clinical Aspects of Hypothyroidism, Can. M. A. J. **20**: 7, 1929.
14. Freeman, E. B.: Chronic Pericardial Effusion in Myxoedema: Report of a Case, Ann. Int. Med. **7**: 1070, 1934.
15. Evans, W.: A Case of Myxoedema With Ascites and Atony of the Urinary Bladder, Endocrinology **16**: 409, 1932.
16. Marzullo, E. R., and Franco, S.: Pericardial Effusion With Myxoedema, Am. Heart J. **17**: 368, 1939.
17. Tatum, L.: Studies in Experimental Cretinism, etc., Proc. Soc. Exp. Biol. and Med. p. 23, 1912.
18. Goldberg, S. A.: Changes in Organs of Thyroidectomized Sheep and Goats, Quart. J. Exp. Physiol. **17**: 15, 1927.
19. Hamilton, W. F., and Brackett, F. S.: Dynamic Consideration on Relation Between Aortic and Ventricular Pressure Curves, Am. J. Physiol. **112**: 130, 1935, and Hamilton, W. F., Woodbury, R. A., and Harper, H. T.: Physiological Relation of Aortic, Radial and Intrathoracic Pressures, J. A. M. A. **107**: 853.

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Department of Reviews and Abstracts

Selected Abstracts

Marchant, E. W., and Jones, H. Wallace: The Effect of Electrodes Made of Different Metals on the Skin Currents. Brit. Heart J. **2**: 97, 1940.

These experiments show the value of tin electrodes in diminishing the amount of the skin currents and suggest that tin is the most satisfactory material for electrodes.

The superiority of tin electrodes did not appear to be due to the fact that they gave a smaller skin current than the others, but rather to this current being much more constant than with the other metals; in consequence when two electrodes were paired the two currents balanced each other.

The surface resistance of tin electrodes is smaller than that of the other metals.

Almost equally good results can be obtained with brass electrodes that have been heavily tin-coated; as these are more easily made and less expensive than the pure tin, they are now being used almost exclusively.

AUTHORS.

Berliner, Kurt: Use of Alpha Lobeline for Measurement of Velocity of Blood Flow. Arch. Int. Med. **65**: 896, 1940.

The alpha lobeline test is a practical method for the measurement of the velocity of blood flow.

Age, sex, and individual variations in nervous irritability are major factors in determining the minimum amount of alpha lobeline required to produce cough; body weight is only a minor factor.

AUTHOR.

Altschule, Mark D., and Iglauer, Arnold: The Effect of Benzedrine (B-Phenylisopropylamine Sulphate) and Paredrine (p-Hydroxy-a-Methyl-Phenylethylamine Hydrobromide) on the Circulation, Metabolism and Respiration in Normal Man. J. Clin. Investigation **19**: 497, 1940.

The effects of benzedrine and paredrine given in doses of 10 to 70 mg. on the metabolism, respiration, and circulation were studied in fifteen subjects with normal cardiovascular systems. The drugs were given by mouth or intramuscularly. In two cases the effect of these drugs was compared to that of epinephrine.

Benzedrine and paredrine in doses of 20 mg. or more caused a marked rise in systolic and diastolic blood pressures in normal man. The cardiac output, pulmonary circulation time, vital capacity, basal metabolic rate, and respiratory dynamics were not changed.

In several instances transitory slowing of the pulse occurred at the onset of the rise in arterial pressure due apparently to a vagal reflex. In some such cases a transitory slight decrease in cardiac output was also detected.

The effects of adrenalin in man were quite different from those of benzedrine and paredrine. They consisted in a slight rise in systolic pressure, no change or a fall in diastolic pressure, marked increase in cardiac output, and shortening of the circulation time.

Benzedrine in doses ordinarily used clinically, i.e., 5 to 10 mg., has no significant effect on the cardiovascular dynamics.

The prolonged pressor action, with no increase of cardiac output and no psychic stimulating effect, suggests that paredrine may be a useful drug in the treatment of certain types of vascular collapse, especially where stimulation of the myocardium may be undesirable.

AUTHORS.

Iglauer, Arnold, and Altschule, Mark D.: The Effect of Paredrine on the Venous System. J. Clin. Investigation **19**: 503, 1940.

Oral, intramuscular, or intravenous injection of paredrine produces a generalized increase of venous pressure in normal man.

Evidence is presented that this increase is due to active constriction of the veins produced by local stimulation.

Venous constriction is not a factor in the production of arterial hypertension by paredrine.

AUTHORS.

McEachern, C. G., Manning, G. W., and Hall, G. E.: Sudden Occlusion of Coronary Arteries Following Removal of Cardiosensory Pathways: An Experimental Study. Arch. Int. Med. **65**: 661, 1940.

The purpose of the present paper is to report the results of experiments which show that the removal of the cardiosensory pathways protects the animal from pain and sudden death after ligation of the coronary artery in the conscious state.

Three groups of experiments were carried out in this series. In the first group partial cardiosensory denervation was produced by removal of the stellate and upper five thoracic ganglions on one side only. Pain was decreased, and the mortality following ligation of the large left circumflex branch was reduced. In the second group, in which complete cardiosensory denervation was produced, ligation of the smaller anterior descending branch resulted in no sudden deaths, and no pain was evidenced. In the third group complete cardiosensory ligation of the large left circumflex branch resulted in a marked decrease in the mortality rate, and again no pain was evidenced.

Removal of the cardiosensory pathways eliminates the pain and markedly reduces the mortality rate after sudden and permanent occlusion of the larger branches of the left coronary artery in the conscious dog.

AUTHORS.

Woodbury, R. A., Murphey, Eugene E., and Hamilton, W. F.: Blood Pressures in Aortic Coarctation: Study of Pulse Contours Taken by the Direct Method. Arch. Int. Med. **65**: 752, 1940.

Direct optical blood pressure tracings were made simultaneously from various arteries of a patient with coarctation of the aorta. Within arteries above the coarctation the systolic pressure was 160 mm. of mercury and the diastolic 88 (mean 113); below the coarctation the pressure was 105 systolic and 82 diastolic (mean 93). Pulse contours recorded from arteries above the coarctation were of normal appearance; from arteries below the coarctation they were flat, smooth, and somewhat delayed. This is the opposite of the variation in contour that occurs normally.

Simultaneous rises in pressure produced in the lower and upper arteries by coughing and straining are discussed in detail.

After injection of epinephrine hydrochloride the pressure rose in the upper arteries, and rose and then fell in the lower arteries. Later it rose in both systems. The records indicate that there was an increase in the resistance of the collateral circulation and peripheral arterioles and an increase in the elasticity of the larger vessels.

Inhalation of amyl nitrite produced changes which were generally the reverse of those produced by epinephrine.

AUTHORS.

Starr, Isaac, and Schroeder, Henry A.: Ballistocardiogram. II. Normal Standards, Abnormalities Commonly Found in Diseases of the Heart and Circulation, and Their Significance. J. Clin. Investigation **19**: 437, 1940.

Ballistocardiograms, i.e., records of the heart's recoil and the blood's impacts, have been obtained on 300 normal persons and over 400 patients. This method requires nothing of the subject save that he lie on the table. No special training is needed by the operator and the time required is about the same as for an electrocardiogram.

The amplitude of the ballistocardiogram is related to the cardiac output. Normal standards for cardiac output have been defined by tests on 200 healthy persons from 20 to 84 years of age.

The form of the ballistocardiogram is determined by the changes of systolic blood velocity in the great vessels. The normal form has been defined. The common abnormalities have been described, their physiologic interpretations set forth, and their clinical significance discussed. The ballistocardiograph makes possible the routine estimation of the amount of the circulation over most, but not all, of the clinical field. It also provides evidence concerning cardiac health or disease of a type not obtainable by other methods.

This method seems particularly adapted to study the course of diseases of the heart and circulation in single individuals, and to assess the influence of therapeutic agents in such conditions.

AUTHORS.

Schroeder, Henry A., and Fish, George W.: Studies on "Essential" Hypertension. III. The Effect of Nephrectomy Upon Hypertension Associated With Organic Renal Disease. Am. J. Med. Sc. **199**: 601, 1940.

Seven patients exhibiting arterial hypertension associated with organic renal disease have been subjected to nephrectomy. Two were markedly improved, and two slightly improved, but all remain actually or potentially hypertensive.

This form of therapy may prove of benefit, but, it seems, only in patients in whom the existence of hypertension is of short duration and in whom arteriolar sclerosis of the other kidney is not advanced. Its use is limited, therefore, to a small number of individuals.

AUTHORS.

Dicker, E.: The Role of the Kidney in the Pathogenesis of Arterial Hypertension. Am. J. Med. Sc. **199**: 616, 1940.

For the kidneys to be able to cause hypertension their circulation must be restricted; all the other renal and urinary manifestations are secondary, independent and incapable of playing a part in the production and maintenance of the hypertension.

AUTHOR.

Mainzer, F., and Krause, M.: The Electrocardiogram in Pellagra. Brit. Heart J. 2: 85, 1940.

Forty-five electrocardiographic records of twenty-three pellagrins with normal circulatory condition have been studied.

In about three-fifths the cardiogram was abnormal. That these abnormalities have a casual relationship to pellagra is demonstrated by the fact that their development is parallel to the clinical course of the disease, and particularly by the rapid disappearance of these changes in some cases subsequent to nicotinic acid treatment.

Tachycardia is mostly encountered at the climax of the disease and bradycardia during the period of convalescence.

The most frequent changes in the electrocardiogram are:

1) low voltage of the ventricular complex,

2) notching of the ventricular complex,

3) deformation of the S-T interval and inversion of the T wave, and, less commonly,

4) shortening of the P-R interval.

These changes are, however, not in themselves characteristic of pellagra. Since Aalsmer and Wenckebach (1929) consider this last characteristic of beriberi, it must be assumed that in pellagra also it may be brought about by a deficiency of vitamin B_1, accompanying the deficiency of the pellagra-preventive-factor.

AUTHORS.

Hahn, L.: The P-R Segment in Hypertensive Heart Disease. Brit. Heart J. 2: 101, 1940.

In 200 electrocardiograms from cases of arterial hypertension, depression of the P-R segment, reaching or exceeding 0.5 mv., was found in 74 per cent of the whole series; in 53 per cent in Lead II or in Leads II and III.

The average systolic pressure was the same in those with and in those without these changes.

The average age of those with these changes in the P-R segment was rather older, and 34 instead of 18 per cent were over 60 years of age.

There was a larger proportion with left ventricular preponderance.

The clinical condition of the heart was rather more severe in the group with these changes.

It is suggested that the changes of the P-R segment in hypertension result from arteriosclerosis of the auricular arteries, causing an insufficient blood supply of this part of the heart muscle.

AUTHOR.

Hunter, Alastair, Papp, Cornelio, and Parkinson, John: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia. Brit. Heart J. 2: 107, 1940.

Nineteen patients having an electrocardiogram with a short P-R interval and a ventricular complex of bundle branch block appearance (Sh.P-R : B.B.B.)—the so-called Wolff, Parkinson, White Syndrome—have been studied, along with three others having a short P-R interval but a normal ventricular complex.

The short P-R interval and bundle branch block syndrome constitutes about 5 per cent of all cases of bundle branch block (140 consecutive cases), and it is found in about 5 per cent of patients who are subject to paroxysmal tachycardia (150 consecutive cases). About three quarters (fifteen out of nineteen) of those with short P-R : bundle branch block had attacks of paroxysmal tachycardia, but only one of the three with short P-R alone had attacks. The charac-

teristic electrocardiogram may be discovered at a routine examination in persons otherwise healthy, in patients with paroxysms of tachycardia, or in those having some other cardiac disease.

Much as in ordinary paroxysmal tachycardia, where most patients are otherwise healthy though some have associated and even causal heart disease, so in this short P-R : bundle branch block syndrome only a minority have organic heart disease (eighteen of ninety reported cases and three of our nineteen cases). Occasionally the causal connection seems to be definite; for instance one patient first showed the characteristic cardiogram soon after acute rheumatism; and examples have been reported after coronary thrombosis. The prognosis seems to be unaffected by the occurrence of the syndrome, even in a patient with associated heart disease.

A remarkable feature is that the same patient may at one time show the typical cardiogram and at another a normal one, both at normal rates. Such switching may be spontaneous, though it may also be induced by exertion or by atropine. It is usually abrupt; only if produced by atropine is it likely to be gradual. The paroxysms of tachycardia are generally supraventricular. Of seven patients whose paroxysms were recorded, five proved to be supraventricular, one supraventricular and at other times ventricular, and one ventricular tachycardia with auricular fibrillation.

A partially isoelectric P in Lead I of a normal tracing with full ventricular complex (near 0.1 sec.) might simulate short P-R : bundle branch block, except that the other leads are normal. On the other hand the slurring of R in a case of short P-R : bundle branch block may in one lead fuse with the P-R period making it isoelectric, and like a normal beat, although the other leads are characteristic of the syndrome.

Bearing on the mechanism of the peculiar electrocardiogram: (a) P often becomes modified in shape when the abnormal cardiogram of short P-R : bundle branch block changes to normal, and this fact alone shows the involvement of a pacemaker that under both conditions can scarcely be a normal one; (b) fixity of the R-T distance with reversion to normal, and the peculiar aspect of the apparent branch block (slurring of the foot of R and rarity of diphasism compared with true branch block) are reasons against acceptance of the syndrome as real bundle branch block.

As these current hypotheses scarcely explain our findings, we are inclined to think that the typical syndrome represents a double rhythm by two interfering pacemakers, one near the sinus and the other in one bundle branch. The modified P preceding the broad ventricular complexes is due to the upper pacemaker; a ventricular extrasystole, arising low in one bundle, quickly interferes and so shortens the P-R interval. The aberrant QRS complex is produced by the ventricular extrasystole and is modified by the QRS of the S-A impulse which reaches the ventricle through the unaffected bundle branch. Intermediate ventricular complexes might be due to the gradual suppression of the ventricular pacemaker. The increased excitability of the conductive system (possibly congenital), responsible for the two pacemakers at a normal rate, is also indicated by the special liability to paroxysmal tachycardia. The subsidiary group, that with short P-R only, are examples of true nodal rhythm.

AUTHORS.

Pollard, H. Marvin, and Harvill, T. Haynes: Painless Myocardial Infarction. Am. J. Med. Sc. **199**: 628, 1940.

In a study of 375 cases of myocardial infarction in which the diagnosis was based on the clinical features, electrocardiographic findings, and available necropsy

material, there were seventeen instances (4.5 per cent) of undoubted coronary occlusion in which no pain, substernal pressure, or other "anginal" symptoms had occurred at any time.

There were fifteen additional cases (4 per cent) in which there had been no pain or anginal symptoms and in which the presence of myocardial infarction was strongly suspected even though the electrocardiographic findings were not pathognomonic. In our opinion painless coronary occlusion is, therefore, relatively uncommon.

Among the symptoms which occurred at the time of the accident in the group of seventeen undoubted cases, the most common were dyspnea, nausea and vomiting, dizziness and fainting or collapse.

AUTHORS.

Lisa, James R., and McPeak, Elsie: Acute Miliary Infarction of the Heart. Arch. Int. Med. **65**: 919, 1940.

An acute lesion of the myocardium called miliary infarction is reported. It was found in ninety-nine cases and was usually associated with the clinical syndrome of sudden left ventricular failure. The material reviewed consisted of 2,857 cases in which autopsy was performed; it was divided into two main groups: 1, cases in which coronary arteriosclerosis was present and 2, cases in which this condition was not present. The first group was subdivided into a cardiac-sclerotic group and a noncardiac-sclerotic group on the basis of clinical symptomatology. The lesion was most frequent in the cardiac-sclerotic group, much less so in the noncardiac-sclerotic group and least frequent in the non-sclerotic group. In the cardiac-sclerotic group its incidence was equal to that of acute coronary thrombosis. The greatly hypertrophied heart with marked sclerosis of the coronary arteries seemed the most susceptible to the occurrence of the lesion.

In seventeen of the ninety-nine cases, thrombi or emboli of the myocardial branches of the coronary arteries were found. The thrombosis was bacterial in one instance and malignant in another. In one case thrombosis of a main coronary artery was caused by a bacterial embolus arising from acute lobar pneumonia. An infectious nature of the myocardial lesion itself was never demonstrated. Infections in other organs, most frequently the lungs, were present in the majority of cases.

It is our opinion that the lesion in the majority of cases is toxic in nature and in a small percentage is due to embolism or thrombosis of the muscular branches of the coronary arteries, usually, even in this group, associated with infection.

AUTHORS.

Spillane, J. D., and White, Paul: Atypical Pain in Angina Pectoris and Myocardial Infarction. Brit. Heart J. **2**: 123, 1940.

Disease of the coronary arteries may manifest itself by paroxysmal, extrathoracic pain on effort. Twelve cases are described in which bouts of pain in one or both arms were, for varying periods of time, the only manifestation of ill health. Such pains, constricting in character, appear suddenly on exertion; they are felt usually at the wrists, forearms, or elbows, and are relieved by rest or nitroglycerine. Fatal attacks may ensue, attacks in which the pain remains located in the arm. In others typical anginal paroxysms or cardiac infarction subsequently develop.

Classical angina pectoris or cardiac infarction is frequently complicated by persistent pain in the shoulder and upper arm. This pain is of a dull, aching

character, diffusely felt, usually on the left side in left-sided and on the right side in right-sided attacks. The pain bears no direct relation to exercise and is not relieved by nitroglycerine. It may precede or follow angina pectoris or cardiac infarction by weeks or even by years. Ten cases are described in which chronic shoulder and arm pain was followed, five months to five years later, by typical angina pectoris. This pain may be incapacitatingly severe during accesses of coronary insufficiency and may then be the outstanding therapeutic problem. Fifteen cases of similar pain following angina pectoris or cardiac infarction are recorded.

The mechanism of the chronic pain is obscure. A local lesion of the shoulder or arm can rarely be demonstrated, though exacerbation of a pre-existing subacromial bursitis may be the explanation in some cases. Often the pain may be interpreted as one of the varied referred phenomena encountered in the arms in angina pectoris and cardiac infarction.

AUTHORS.

Micks, R. H.: Congenital Aneurysms of All Three Sinuses of Valsalva. Brit. Heart J. 2: 63, 1940.

A case is described in which aneurysms, or more correctly gross dilatations, of all three sinuses of Valsalva were present.

The left ventricle was considerably hypertrophied, but apart from this and the aneurysms the heart was healthy. There was no evidence of syphilis or endocarditis, recent or old-standing. There were no perforations or abnormal communications between the chambers of the heart.

The aneurysms were deep (nearly 5-0 cm.) pocket-like extensions of the sinuses of Valsalva in a downward direction. They excavated the smooth-walled part of the ventricle described as the aortic vestibule, but not the thick trabeculated portion of the wall. Their symmetry, their endocardial lining, and the absence of syphilitic or ulcerative changes were strongly suggestive of a congenital abnormality.

The aneurysm of the left sinus measured over 60 c.c. in volume. It formed a prominence on the surface of the heart to the left of the pulmonary artery.

The aneurysm of the right sinus measured 15 c.c. in volume. It bulged into both the right auricle and the right ventricle. The presence of this aneurysm in the interventricular septum is believed to have produced the heart block from which the patient died.

The aneurysm of the posterior sinus measured 9 c.c. in volume. It bulged into both the right and left auricles.

The patient was free from symptoms of heart disease till a few months before his death. He died from acute cardiac failure and complete heart block, and during his last illness several interesting disturbances of rhythm occurred.

Records of three other cases of aneurysm of all three sinuses of Valsalva have been found and discussed. In all the degree of dilatation was considerably less than in the case here recorded, and the direction of the excavation appears to have been different.

AUTHOR.

Braunstein, Albert L., and Townsend, Stuart R.: Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis. Arch. Int. Med. 65: 957, 1940.

The clinicopathologic observations of bacterial endocarditis (acute and subacute) superimposed on syphilitic aortic valvulitis are presented in detail.

To the eleven cases found in the literature, nine of our own have been added, the total of twenty "proved" cases including seven of acute and thirteen of subacute endocarditis.

That the diagnosis may be concomitant existence of the two conditions may be suspected when in the presence of syphilitic aortic valvular insufficiency a gradually progressive anemia exists with slight daily intermittent rises in temperature which cannot be explained by any other observations. Frank evidence of bacterial endocarditis in the presence of syphilitic aortic insufficiency usually bespeaks the involvement of a valve other than the aortic.

The pathogenesis of bacterial endocarditis is discussed in relation to our nine cases, and possible reasons for the infrequency of the simultaneous occurrence of syphilitic aortic valvulitis and bacterial endocarditis are presented.

AUTHORS.

Gross, Harry, and Engelberg, Hyman: Essential Hypertension. A Comparison of the Hypertensive and Non-Hypertensive Phases Following Coronary Thrombosis. Am. J. Med. Sc. **199**: 621, 1940.

An analysis is presented of 100 autopsied cases of hypertension, and severe coronary artery disease studied for the effect of the blood pressure on the subsequent course. All the cases had cardiac hypertrophy and marked myocardial damage.

Ninety cases had chronic congestive heart failure. The high incidence of heart failure is due partly to the type of patient admitted to Montefiore Hospital. The onset of heart failure frequently followed an acute coronary occlusion. This occurrence was so striking that in cases of chronic coronary sclerosis when heart failure begins rather abruptly a silent coronary occlusion should be suspected.

There were twenty-four cases with terminal acute coronary closure and in these the course of blood pressure was known for at least one year prior to death. Fifteen had hypertension persisting up to the final closure, seven had low blood pressure for several months prior to the closure and in two the blood pressure varied in the preceding year.

Analysis of the course of blood pressure subsequent to acute coronary occlusion was made. Eighteen cases had persistent hypertension (after recovery from the initial drop), twelve had permanently low blood pressure, and in ten the pressure varied. The same variations in the course of hypertension occurred when no acute occlusion could be diagnosed clinically with certainty.

Twenty-one of the 100 cases died suddenly. Many of these had the clinical picture of acute coronary thrombosis but in only four of this group was a terminal closure found following coronary thrombosis.

The subsequent blood pressure in hypertensive cases following coronary thrombosis had no effect on longevity, or on the occurrence, severity, and duration of heart failure. Neither was there a definite relation between the course of blood pressure and the heart weight and the duration of failure. Physiologic factors undoubtedly play a role in adjusting the work of the heart to a restoration or a permanent fall in the blood pressure. These factors have been discussed.

AUTHORS.

Nesbit, Reed M., and Ratliff, Rigdon K.: Hypertension Associated With Unilateral Nephropathy. J. Urol. **43**: 427, 1940.

Numerous cases of hypertension have been reported associated with chronic sclerosing pyelonephritis, both unilateral and bilateral. Vascular changes within

the infected kidney associated with hypertension have been reported by most observers. The authors present several cases exhibiting these same vascular changes in chronically infected kidneys without associated hypertension.

Nephrectomy appears to be a justifiable procedure in cases of unilateral pyelonephritis with associated hypertension, with reasonable hope for improvement provided the functioning capacity of the remaining kidney is unimpaired.

SCHWARTZ.

Blalock, Alfred: Experimental Hypertension. Physiol. Rev. **20**: 159, 1940.

This is a comprehensive review of experimental hypertension, particularly that produced by renal ischemia.

NAIDE.

Leuth, Harold L.: Thrombosis of the Abdominal Aorta. A Report of Four Cases Showing the Variability of Symptoms. Ann. Int. Med. **13**: 1167, 1940.

Four cases dying from thrombosis of the abdominal aorta are reported. The youngest was a man of 45, who, for many years, had had rheumatic heart disease with aortic and mitral valvular disease and auricular fibrillation. Pathologically there was extensive atheromatous degeneration of the aorta. The second case, a 56-year-old male, dying 36 hours after the amputation of his second leg, showed at post mortem, extensive sclerosis of the aorta, with a saddle thrombus extending into the iliacs, a thrombus in the inferior vena cava, and a bronchogenic carcinoma of the lung. The other two cases were 71 and 80 years old respectively, with high grade atherosclerosis of the abdominal aorta. While thrombosis of the aorta is not a common condition, nevertheless it is not such a rare disease that it cannot be recognized ante mortem.

MCGOVERN.

Conner, Lewis A.: Thrombophlebitis and Its Pulmonary Complications. New England J. Med. 222: 125, 1940.

This is a report of 1,540 cases of typhoid fever with phlebitis occurring in the author's experience, at the turn of the century, when typhoid fever was a major health problem in New York City. He states that of this group of 1,540 cases there were sixty-three cases with suggestive evidence of pulmonary embolism. There is nothing new in this paper, except perhaps the mention of heparin as an anti-coagulant.

MCGOVERN.

Dick, G. F., and Freeman, G.: Temporal Arteritis. J. A. M. A. **114**: 645, 1940.

Two cases of temporal arteritis in elderly females are reported. This disease is a chronic inflammatory process, involving the temporal arteries, with extension to the other vessels of the scalp, face, arms, and retinae; it is self-limited, lasting several months. There is a characteristic pathologic picture in which giant cells are a prominent feature. Photomicrographs accompany the description.

MCGOVERN.

Crile, G., Jr., and Newell, E. T.: Abdominal Apoplexy: A Spontaneous Rupture of a Visceral Vessel. J. A. M. A. **114**: 1155, 1940.

A patient with severe essential hypertension and advanced arteriosclerosis had spontaneous abdominal apoplexy four days after a celiac ganglionectomy was performed. On operation a large hematoma was found lying between the leaves

of the mesocolon and involving the transverse colon for a distance of six inches. The patient recovered but succumbed one month later to a cerebral hemorrhage following extraction of a tooth. References are given to ten cases of abdominal apoplexy associated with arteriosclerosis and hypertension which have been previously reported.

McGovern.

Neiman, Benjamin H., and Marks, Meyer B.: Productive Aortitis With Multiple Aneurysms in a Child. Am. J. Dis. Child. **59**: 571, 1940.

A case of productive aortitis with four thoracic aneurysms in an 11-year-old girl, is presented in detail. Syphilis is suggested as a cause, but no congenital stigmata of syphilis were shown to exist.

Schwartz.

Fallis, L. S.: Mesenteric Thrombosis Operation: Recovery. Report of Two Cases. Am. J. Surg. **47**: 128, 1940.

The report deals with mesenteric thrombosis in two males of 25 and 60 years of age, respectively, with extensive gangrene of the small intestine, resection of the gut and recovery. The most outstanding clinical symptom was abdominal pain. The vomiting that accompanied the pain was of secondary importance in making the diagnosis.

Schwartz.

Dunphy, J. Englebert, and Whitfield, Robert D.: Mesenteric Vascular Disease. Am. J. Surg. **48**: 632, 1940.

The etiology and pathology of mesenteric vascular disease are reviewed briefly, the clinical manifestations are discussed in detail, and certain points in the surgical management of these cases are outlined.

The etiologic factors involved in mesenteric vascular disease are considered to be not sufficiently clear to be of use in diagnosis.

Usually the pathogenesis and gross pathologic anatomy of arterial and venous mesenteric vascular occlusions is similar, with slowly progressing or sudden onset. Thus clinical differentiation is unreliable except for a fortuitously obvious etiologic factor.

Clinical manifestations may be divided into three groups: those which result from spasm or small occlusions of mesenteric arteries, so-called "abdominal angina," or "abdominal intermittent claudications"; those which follow an extensive occlusion of either a mesenteric artery or vein; and those which follow a result of rupture of a sclerotic artery with intraperitoneal hemorrhage, "intra-abdominal apoplexy."

Schwartz.

Oard, Harry C., Campbell, C. Russell, and Dealy, Frank N.: Traumatic Complications in Peripheral Vascular Disease. Am. J. Med. Sc. **199**: 194, 1940.

Because of the altered physiology in extremities afflicted with obliterating arterial disease, many ordinary therapeutic measures cause injury and produce open lesions. Since development of open lesions on poorly nourished limbs entails great economic loss, prolonged morbidity, and a high death rate, every effort should be made to eliminate trauma in patients with peripheral vascular disease.

Schwartz.

King, E. S. J.: A Single Coronary Artery. Brit. Heart J. 2: 79, 1940.

A case of a "single" right coronary artery has been described and also its distribution to the myocardium. The large artery immediately divided into three branches. The main vessel took the usual place of the right coronary artery and of most of the circumflex branch of the left coronary artery. The intermediate vessel took the place of an anterior branch of the right coronary artery. The third, passing along the usual site of the small conus anastomosis, took the place of the anterior descending branch of the left coronary artery.

AUTHOR.

Kile, R. L., and Rusk, H. A.: A Case of Cold Urticaria With an Unusual Family History. J. A. M. A. 114: 1067, 1940.

In an unusual case of allergy to cold, in which therapy was unsuccessful, the interesting point is made that of forty-seven members of the family, twenty-three gave history of urticaria.

McGOVERN.

Smithwick, Reginald H.: Surgery of the Sympathetic Nervous System With Particular Reference to Vascular Disease. New England J. Med. 222: 546, 1940.

An evaluation of the procedure of interruption of sympathetic pathways in man leads the author to the conclusion that sympathetic denervation of the extremities is particularly useful for circulatory disorders such as Raynaud's disease, certain cases of thromboangiitis obliterans, certain of the causalgias, arterial embolism, scalenus anticus syndrome, and in some cases acute thrombophlebitis of femoral and iliac veins. In extreme hyperhydrosis sympathectomy often yields impressive clinical results. Although excellent results have been reported, the true value of sympathectomy as a form of treatment of essential hypertension in man will not be known for several years. Paravertebral alcohol injection is preferred for treatment of intractable angina pectoris because of the lower mortality than sympathectomy.

SCHWARTZ.

Gross, Robert E., Emerson, Paul, and Green, Hyman: Surgical Obliteration of a Patent Ductus Arteriosus in a Seven-Year-Old Girl. Am. J. Dis. Child. 59: 544, 1940.

Most patients with patent ductus arteriosus show little or no disability during childhood, although atheromatous plaques may be built up in the pulmonary artery, which may later be the site of bacterial vegetations. The patent ductus may so exert the heart that decompensation occurs later. These sequelae may be avoided if operative ligation of the ductus can be performed early in life. Four such patients have been successfully subjected to this procedure without mortality and without complication. One of these cases is here reported in detail.

McGOVERN.

Ochsner, Alton, and Smith, Marvin C.: The Use of Vitamin B_1 for the Relief of Pain in Varicose Ulcers. J. A. M. A. 114: 947, 1940.

The oral administration of vitamin B_1 to ten patients with painful varicose ulcers resulted in complete relief of symptoms in eight.

NAIDE.

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